Nathalie Roche (°1967) studeerde van 1985 tot 1992 Geneeskunde aan de Erasmus Universiteit te Rotterdam in Nederland. Zij deed haar opleiding in Algemene Chirurgie en Plastische Chirurgie in Nieuwegein, Gouda, Amsterdam en Gent en behaalde in 2000 het diploma van Plastisch, Reconstructief en Esthetisch Chirurge. Zij werd benoemd tot fellow van het Collegium Chirurgicum Plasticum. Tevens legde zij het Europees examen Plastische Chirurgie af en werd fellow of the European Board of Plastic, Reconstructive and Aesthetic Surgery. Van 2001 tot begin 2004 was zij als voltijds staflid werkzaam op de afdeling Plastische, Reconstructieve en Handchirurgie van het Erasmus Medisch Centrum te Rotterdam, Nederland, waar zij zich verder bekwaamde in kinder plastische chirurgie, hoofd- en halsreconstructies en craniofaciale chirurgie. Vanaf 2004 is zij voltijds werkzaam als Adjunct-Kliniekhoofd in de Kliniek voor Plastische Heelkunde in het Universitair Ziekenhuis te Gent.
Nathalie Roche is auteur en mede-auteur van talrijke publicaties in diverse nationale en internationale beroepstijdschriften. Als spreekster geeft ze regelmatig voordrachten in België en Nederland en op internationale congressen. Zij is actief als vrijwilligster in missies naar ontwikkelingslanden, onder andere naar Indonesië, waar zij voornamelijk reconstructies uitvoert van aangeboren aangezichtsafwijkingen en brandwondenletsels.
Haar aandachtsgebieden zijn kinder plastische chirurgie, craniofaciale chirurgie, microchirurgie en hoofd- en halsreconstructies.

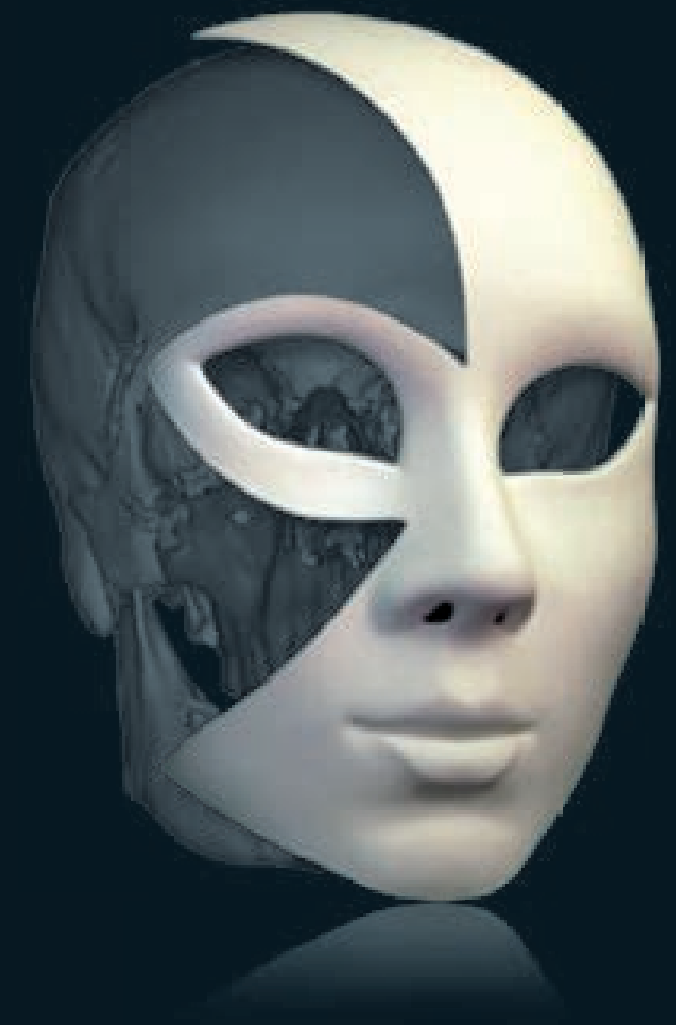
Face Off Multidisciplinary Approach to Facial Transplantation

Transplantatie van lichaamsdelen opgebouwd uit weefsels van embryonaal verschillende oorsprong staat bekend als transplantatie van samengesteld weefsel (Composite Tissue Allotransplantation, CTA); aangezichtstransplantatie is een voorbeeld hiervan. Door deze techniek is het mogelijk uiterst gespecialiseerde structuren, die op geen enkele andere manier te herstellen zijn, te reconstrueren in 1 operatie bij patiënten met complexe en verminkende aangezichtsafwijkingen. Wereldwijd werden sinds november 2005 34 van dergelijke ingrepen uitgevoerd.
Na een voorbereidende fase van 3 jaar werd in december 2011 de eerste aangezichtstransplantatie (# 19 wereldwijd) in het Universitair Ziekenhuis te Gent, België uitgevoerd. Dit proefschrift behandelt de multidisciplinaire aanpak van aangezichtstransplantatie.
De doelstelling was het beschrijven van de chirurgische, ethische, immunologische, psychologische en revalidatie aspecten; tevens was het de bedoeling bewijs te leveren voor het feit dat succes bij het uitvoeren van aangezichtstransplantaties afhankelijk is van een goed geleid multidisciplinair team, adequate screening en selectie van de potentiële kandidaat door dit team en de juiste indicatiestelling voor deze operatie. Zoals geldt voor elk ander complex medisch probleem, is de enige manier om een levensveranderende procedure, die geassocieerd is met vele mogelijke medische complicaties, te rechtvaardigen het opdoen van ervaring en het verzamelen van objectief bewijs door het opzetten van gecentraliseerde en gespecialiseerde centra, waar alle noodzakelijke expertise aanwezig is. In deze setting zal aangezichtstransplantatie een geaccepteerde ingreep worden die hoop en een nieuwe toekomst kunnen geven aan patiënten met een ernstige en verminkende aangezichtsafwijking. De bevindingen van dit proefschrift komen overeen met de rapporten van andere centra en zullen hopelijk in de toekomst bijdragen tot het optimaliseren van de uitkomsten van aangezichtstransplantaties en het bepalen van de exacte indicatie voor deze ingreep.

Face Off
Multidisciplinary Approach to Facial Transplantation
Nathalie Angèle Roche MD

Face Off

Multidisciplinary Approach to Facial Transplantation



Nathalie Angèle Roche MD

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Faculty of Medicine and Health Sciences

Department of Plastic and Reconstructive Surgery

Face Off
Multidisciplinary Approach to Facial Transplantation

Nathalie Angèle Roche, MD

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Doctor of Philosophy in Health Sciences

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To my parents, for their ever lasting and loving support

To my three precious pearls, the sunshine of my life

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Invited preface by Dr. M.P. Carpentier Alting

It is rare to meet extraordinary people, but I can surely say that Nathalie is one of them.

We first met when I was seated in an auditorium waiting for a double dissertation defense ceremony to begin in Rotterdam twenty odd years ago.

A young lady took a seat on my right and I was struck by her presence and the energy she radiated.

During the public discussion we got talking, in fact whispering, and to my delight I found out that she wanted to become a plastic surgeon.

Her energy, drive and determination were instantly clear to me and, still whispering, I offered her a job for 1 year on the spot as our assistant in the plastic surgery department.

I was absolutely sure that she would fit in our practice, would be a quick learner and that we would find a suitable place for her plastic surgery training.

Time proved we were both right and my eagerness was passed on to the next generation.

What a pleasure and joy to have had such an opportunity.

Menso Carpentier Alting

Imagination is the highest form of research.

The only real valuable thing is intuition.

Albert Einstein

Part 1

General Introduction

CHAPTER 1

History and update on facial transplantation

Based on:

Nathalie A. Roche, Phillip N. Blondeel, Kristiane M. Van Lierde and Hubert F. Vermeersch. History and update on facial transplantation. *Acta Chir Belg 2015;115(2):99-103.*

Abstract:

Background:

Composite tissue allografting (CTA) represents the essence of reconstructive surgery, combining principles of solid organ transplantation (SOT) and modern plastic surgery techniques. The purpose of this article is to give a review of the history of facial CTA and an update of the cases that have been operated so far worldwide.

Methods:

A systematic review of the medical literature was performed. Twelve relevant publications were selected and analyzed for clinical data of the patients, surgical aspects of transplantation, complications and outcome. Additional data on the experience with face transplantation were collected based on media reports.

Results:

The past 9,5 years, 34 face transplants have been performed worldwide. The main indication was posttraumatic deformity. In all cases standard triple drug immunosuppression as in SOT was successfully used and at least 1 period of acute rejection was seen in all patients, controllable with conventional immunosuppressive regimens. Overall functional outcomes are good and satisfaction rate is high, surpassing initial expectations. The main complications are opportunistic infections; 5 deaths occurred.

Conclusions:

Facial CTA is a life changing procedure and has led to new treatment options for patients with complex, devastating and otherwise non-reconstructable facial deformities to restore appearance and overall well-being in a single operation. The key to success lies in the selection of the appropriate patient, who is stable, well-motivated and therapy compliant. Thorough screening and follow-up by a multidisciplinary team, well prepared surgical approach and intensive, early rehabilitation are all crucial factors for minimizing complications and ensuring a safe and rapid recovery.

Key Words

Facial transplantation; Composite tissue allotransplantation; Complex facial defects.

Abbreviations

CTA = Composite Tissue Allotransplant(ation)

SOT = Solid Organ Transplantation

FT = Face/Facial Transplant/Transplantation

Disclosure

None of the authors has any financial conflicts of interest in the publication of this article.

History of human composite tissue allotransplantation

Transplantation of body structures composed of multiple tissues derived from ectoderm and mesoderm is known as composite tissue allotransplantation (CTA). CTA includes structures such as hand, face, larynx, joints and abdominal wall; this in contrast to solid organ transplantation (SOT) such as heart, lung, kidney, which have a relatively uniform structure. Unlike SOT, that is life saving in most cases, the goal of CTA is to restore functional loss and to improve quality of life. Also in SOT, the organ is fully functional at the time of revascularization; this in contrast with CTA where nerve regeneration into the transplanted tissues is required for reestablishment of sensation in the skin and recovery of muscle function. CTA is the dream of reconstructive surgeons as massive defects of the face and extremities are nearly impossible to reconstruct with original tissue and highlights the historical connection between plastic surgery and allotransplantation.

During many centuries, physicians have been striving for replacing lost limbs and facial tissues. Very known is the legend of the third century twin saints Cosmos and Damian replacing an ulcerated leg of an esteemed churchman with a leg of a recently deceased Ethiopian (1). In the 16th century, Gaspare Tagliacozzi reconstructed a nose using a flap of forearm tissue donated by a slave (2). Obviously, all ancient transplantation attempts failed due to rejection and inadequate surgical techniques.

At the beginning of the 20th century, French surgeon Alexis Carrel developed a method of coapting small vessels using fine needles and sutures and performed successful orthotopic hind limb transplant in dogs (3). At the same time, Charles Guthrie of the University of Chicago described heterotopic allotransplantation of dog heads (4). In 1908 Judet and Lexer performed the first whole joint transplantations in animals and humans, however as the grafts were nonvascular and immunosuppression was not used, viability was discussable (5, 6).

All these studies showed the technical feasibility of transplantation and surgeons continued to experiment. They focused their efforts on kidney because of its relatively simple anatomy and in 1933 Yurii Voronoy performed the first human kidney transplant in Russia; the graft unfortunately failed due to rejection (7).

During World War II, the pioneering experiments of biologist Peter Medawar and plastic surgeon Thomas Gibson in skin and composite tissue allografting for reconstruction of severely burned soldiers led to a major breakthrough in the development of modern transplant immunology (8). Medawar demonstrated specific characteristics of the immune response and discovered the acquired immune tolerance, the phenomenon underlying discrimination self from non-self, suppressing allergic responses, allowing chronic infection instead of rejection and elimination and preventing of attack of the fetus by the maternal immune system.

The observations of the high immunogenicity of skin in experimental allotransplantations turned the efforts of researchers to other possibilities and renal allotransplantation seemed the most promising. In 1954, a team led by plastic surgeon Joseph Murray performed the first successful human kidney transplant in Boston USA between identical twins (9).

In 1957 the first successful nonvascularized human allograft consisting of an en bloc digital flexor tendon mechanism was performed by visionary plastic surgeon Erle Peacock, who introduced the term composite tissue allograft (10). In 1959, the team of Murray succeeded in the first kidney allograft between fraternal twins using total body irradiation (11). In the early 1960's, 2 major breakthroughs addressed the rejection problems. It became possible to closely match the donor and recipient tissues. Furthermore the development of the immunosuppressant azathioprine (Imuran) and its clinical introduction by Murray and Calne largely increased the transplant success rate (12, 13).

After successful renal allografts, Robert Gilbert transplanted the first hand CTA in 1964 in Ecuador, using azathioprine and prednisone for immunosuppression. Although technically successful, graft rejection and failure occurred after 3 weeks (14). Shortly after Gilbert's attempt, Peacock and John Madden nearly succeeded with a hand transplant between identical twin sisters, however the recipient canceled the procedure last minute because of psychological stress of "wearing" her sister's hand. This event highlights the role of identity and psychological issues in CTA reappearing 35 years later in the ethical debate around hand and face CTA (15). Further progress in SOT was booked with first pancreas in 1966 by Lillehei and Kelly in Minnesota USA, first liver by Starzl in

1967 at the University of Colorado USA, first heart in 1967 by pioneer Christian Barnard in Capetown South Africa and first heart-lung in 1981 by Reitz and Shumway at Stanford University Medical Center USA (16).

In 1969 Kluyskens and Ringoir performed the first laryngeal CTA in Belgium; this was an avascular transplant that failed after 8 months when immunosuppression had to be ceased for tumor recurrence leading to fatality (17). The early outcomes of skin and skin-bearing transplants together with failures in experiments led to the conclusion these structures were too antigenic for transplantation and this was insurmountable by immunosuppressiva. No clinical successes were reported for 35 years after the first human CTA (15).

Only in the early 1970's and 1980's, calcineurin inhibitors appeared with the discovery of cyclosporine and tacrolimus respectively. It was found out that these drugs were more effective when used with steroids. Solid organ graft successes greatly increased and the new drug regimens also showed positive effects in animal CTA experiments. In the mid 1990's, a new drug, mycophenolic acid appeared; when combined with calcineurin inhibitors, it produced repeatable and long-term survival of skin-bearing CTA in animals (15).

Ultimately in 1998 the first successful hand CTA was performed in Lyon France by a team led by Jean-Michel Dubernard using tacrolimus/mycophenolate mofetil/corticosteroids combination therapy; other successful hand CTA's followed in Louisville USA and China (15, 18). More experiments were conducted and in 1998 Strome and co-workers in Cleveland USA performed the first successful laryngotracheal CTA. In Germany Hofman transplanted a vascularized knee joint (19, 20). Since then international CTA programs were organized and vascularized graft types were expanded to include face, abdominal wall, peripheral nerve, joints, scalp, uterus and penis. In 2003 surgeons in Nanjing China transplanted a large flap of posterior scalp, neck and both ears in a 72-year-old woman after resection of a large malignant melanoma. Survival was only 4 months and the event went relatively unnoticed by the media (21). Finally the world first successful face transplant (FT) was performed in November 2005 in Amiens France (22). In 2014 the first healthy baby was born after a uterus-transplantation performed in Gothenburg Sweden by a team led by Brännström in 2013 (23).

Human face as an organ

The face is a unique part of human anatomy that like no other feature is associated with special qualities that makes us specifically human. Normal facial anatomy is not only required for many sensory functions such as vision, smell and taste, hearing, but also for mastication and breathing. As importantly, an intact face is essential for verbal and non-verbal communication. Of all physical handicaps, none is more devastating than facial disfigurement. It severely affects social interactions and one's perception of self-image often leading to psychological problems including suicide, discrimination by others and exclusion from society and normal life. Seen in this context, the face should be considered as a vital organ and has been recognized as such by health departments in USA and France. This recognition has transformed facial CTA from an experimental to an accepted procedure equal to SOT (24, 25).

The evolution of facial reconstruction

Defects of the face can be present from birth (congenital) where the original tissues never existed. Acquired defects of the face are much more common and are caused by trauma (burns, crush injuries) or tumors (benign or malignant). Worldwide million of patients are present with severe craniofacial deformities requiring reconstruction for restoration of functional, aesthetic or both deficits. The development of modern facial plastic surgery started during both World Wars. Hippolyte Morestin, Harold Gillies and Archibald McIndoe were all plastic surgeons involved in treating war victims with facial deformities; they developed many techniques in facial reconstruction that are still in use today. In the 1950's Ralph Millard developed new techniques to repair cleft lip and palate and in the 1960's, Paul Tessier showed breaking through techniques that were a major advance in craniofacial surgery. The field of reconstructive microsurgery was explored in the late 1970's based on the work of Harry Buncke, making it possible to transplant tissues from one part of the body to the other (26).

Until 2005, methods of reconstructing severe facial defects consisted of repairing or reattaching original tissue, transferring autologous tissues or using prosthetic materials. The best results are achieved when the original tissues can be salvaged and used; in 1994 using modern microsurgery techniques, Abraham

Thomas in India conducted the first full face replantation in a 9-year-old girl whose face and scalp were pulled of when her hair was caught in a tresher. Unfortunately these cases are very rare. Most patients with severe, especially centrally located facial deficits, require multiple complex procedures with autologous tissues over periods of years which fill in the defect, but, due to the absence of specialized facial tissues and structures (such as orbicularis oris and oculi muscle, nose, lips, eyelids), often result in little or no functional recovery, poor aesthetic outcomes and donor sites (where tissues were taken) with major problems such as scarring and pain. In cases where surgery is not possible due to various reasons, prosthetic materials can be used to cover and/or camouflage the defect, but they provide static appearance and no functional or dynamic return (27, 28).

Facial transplantation (FT) makes it possible to use healthy facial tissues, identical to the recipient's original tissues to reconstruct the defect in a single operation providing an aesthetic and functional satisfying result. The technical expertise and techniques needed to execute this operation are based on modern microsurgery and craniofacial surgery, done frequently and on routine basis in centers were complex craniofacial reconstructions are performed (27).

Worldwide the debate by scientific and lay communities around technical, immunological and ethical issues of FT already started in 2000 (29). As stated above, facial transplantation is, in contrast to SOT, not a life saving but a life changing procedure and a vital element for quality of life making it possible for patients to reintegrate into society and resume normal lives. Patients who are candidates for FT are in general physically healthy patients (unlike SOT patients) without major comorbidities; they must be willing to undergo lifelong immunosuppression with all possible consequences such as cancer, metabolic diseases, opportunistic infections, even death and follow rehabilitation programs after surgery. These consequences must be carefully balanced and patients must be thoroughly screened before undergoing such a procedure. In case of graft failure, the recipient in some cases has no other option than another face transplant (especially after multiple previous reconstructions and depletion of available donor sites on the body) and the graft cannot simply be removed without life-threatening consequences. Multidisciplinary team approach and programs on FT are mandatory (28 - 32).

In 2002 plastic surgeon Peter Butler in the UK was the first to suggest facial transplantation to the public as a possibility for facial severely disfigured patients. This assumption created a complete media circus and a working party on FT was formed in the UK, obtaining approval to perform FT in 2006; until now however, no cases have been reported in the UK. Meanwhile teams from Louisville USA (Barker et al.), Paris France (Lantieri et al.) and Cleveland USA (Siemionow et al.) were already working on defining ethical guidelines, outlining immunological and anatomical aspects of FT in animal experiments and human cadavers and developing multidisciplinary teams for establishing programs on human face transplantation (29, 30, 32, 33).

In November 2004, based on the life work of Maria Siemionow, the Cleveland Clinic in Ohio USA received the world's first Institutional Review Board protocol approval for face transplantation in humans (34, 35). In 2002 Lantieri and co-workers in Paris France applied a request to the government's advisory council on bio-ethics for facial repair using a composite tissue allograft in highly disfigured patients. In 2005 the clinical research protocol, developed after many preclinical studies to assess immunological, psychological and functional aspects of facial transplantation, was approved by the French Agency for the Sanitary Safety of Health Care Products making this procedure possible in France (32).

In November 2005 the world's first partial face transplant was performed by a different team led by Devauchelle and Dubernard in Amiens France. The recipient suffered loss of lips, nose and central cheeks from a dog bite. Until now, the transplant is still successful with full recovery of sensory and motor function (36). Since then a total of 34 face transplants has been performed worldwide (37, 38); our team performed the 19th face transplant in December 2011 in Ghent, Belgium (39). The possibilities of CTA are broad. In May 2015, the world's first partial skull and scalp transplant along with a pancreas and kidney was carried out in Texas USA in a 55-year-old man suffering from diabetes since age 5 and a large head wound caused from cancer treatment (40).

Update on the first 9,5 years of facial transplantation

A systematic review of the peer-reviewed medical literature was performed of the medical database PubMed (Medline) using following search terms: face; facial; transplant; transplantation; composite tissue allotransplant and vascularized composite allotransplant; the time frame was between 2004 and 2015. Articles were in English language and contained at least one case report of FT. Twelve relevant overview reports were selected and analyzed for clinical data of the patients, surgical aspects of transplantation, complications and outcomes. As only 2/3 of the world-wide performed cases have been reported in the medical literature, additional data on the experience with face transplantation were collected based on media reports and professional meetings on facial transplantation.

Between 2005 and 2010, 13 face transplants have been performed and from 2011 until now, another 21 patients underwent this procedure. These numbers show that facial transplantation has become a clinical reality and a relatively common surgical procedure after many technical, logistic and social aspects have been resolved. Different authors have reviewed face transplant cases, highlighting surgical, immunological, functional, psychological and ethical aspects (24, 26, 28, 29, 37, 41 - 48).

Table 1.1 and 1.2 provide a description of all face transplants with patient details.

A total of 34 patients have been operated on, 27 males and 7 females (79% vs 21%). As a single center, the largest series of 7 transplants were performed by the team led by Lantieri in Hôpital Henri Mondor Créteil Paris France and by the team of Pomahac at Brigham and Women's Hospital in Boston USA (also 7 patients). Ozkan in Akdeniz University Hospital Antalya Turkey transplanted a total of 5 patients.

The amount of tissue transplanted varied: 19 procedures were partial and 15 full face; in 23 cases the graft was osteocutaneous. The indications were traumatic injury in 27 cases (ballistic trauma n=15, burns n=8, animal bites n=3, industrial accident n=1), neurofibromatosis in 4 cases, facial deformity after tumor resection in 2 cases; in 1 case the origin of the defect was not reported.

Essential requirements for successful facial transplantation are craniofacial and microsurgical techniques (2). These techniques are routine in centers were complex facial reconstructions are performed. No microsurgical complications were reported. In the first osteocutaneous grafts issues were encountered with the fitting in the recipient; refinements in technologies such as computer-assisted design and modeling, intraoperative navigation and premanufactured cutting guides helped resolving these problems (39, 47). Operation time ranged from 15 to 25 h, including procurement of the graft. The amount of blood loss seems to be directly related to the extent of reconstruction (partial, full, with or without bone) and the underlying disease. All teams used a custom-made resin mask for reconstitution of the face of the donor.

Table 1.2 provides an overview of the immunosuppressive drug therapy, treatment of rejection and complications in reported FT cases. In all cases the gold standard triple drug immunosuppressive regimen as in clinical kidney transplantation was applied consisting of steroids, calcineurin inhibitors (tacrolimus) and antimetabolites (mycophenolate mofetil). Antithymocyte globulin was used for induction in almost all cases. Acute rejection occurred in all cases within the first year of transplantation; no cases of chronic rejection or chronic allograft vasculopathy have been reported yet, this in contrast to this phenomenon in hand transplantation. No graft versus host disease has occurred. In the minority of cases a sentinel skin flap from the donor was transplanted for monitoring and surveillance biopsies. In some cases this flap was a good indicator of rejection, whereas in other cases it was not (47, 49).

Sensory recovery has been good with satisfactory restoration by 8 months (recovery of heat and cold sensation, response to painful stimuli, discrimination of light touch and localized two-point touch discrimination). This can occur even in patients with extensive nerve damage in whom nerve repair is not possible. Tacrolimus has a beneficial side effect of accelerating axonal nerve regeneration, which is favorable especially in these cases. Restoration of motor recovery has been slower; it requires facial nerve coaptation and can be very difficult as structures are often damaged and scarred. It occurs typically by 6-8 months with ongoing improvement in the following years. All recipients recovered the ability to smell, eat, drink, smile and speak; the removal of scarred tissue has the additional benefit of reducing chronic pain. The use of an early and intense rehabilitation program is indicated and includes speech therapy, range of motion exercises and sensory re-education. These measures expedite cortical reorganization in patients, promoting recognition and integration of the newly transplanted muscles into the patient's motor cortex. Such brain plasticity contributes to favorable outcomes after FT (37, 39).

Despite standard antibacterial medication and viral prophylaxis protocols, opportunistic infectious complications have been common such as cytomegalovirus (CMV) activation, herpes simplex, herpes zoster, Epstein-Barr virus (EBV), *Candida,* rosacea, staphylococcal infection, *Enterobacter, Pseudomonas Aeruginosa* (see table 1.2). Other complications included chronic renal insufficiency, new onset diabetes and gastro-intestinal side effects. Neoplasia was seen and treated successfully in 2 patients (cervical dysplasia and B cell lymphoma). Mortality has been reported in 5 cases (15%). The 1st death occurred in China due to non-adherence to the immunosuppressive regimen 2 years after surgery. In France a patient died 2 months due to general infectious sepsis after total face and bilateral hand transplantation. The 3rd case was a Spanish patient undergoing transplantation after treatment for head and neck cancer who had a recurrence 4 years postoperatively leading to death. In Turkey 1 patient died 1 year postoperatively due to organ failure necessitating removal of the transplanted face. The most recent reported death was a few months ago in France in the series of Lantieri where the 7th patient committed suicide 4 years after surgery (Lantieri, personal communication).

Psychological outcomes have been generally favorable with improvement on quality of life, lower anxiety and depression levels, improved body image, sense of self-esteem and social reintegration. Several patients returned to work. Despite earlier concerns regarding identity transfer of the donor to the recipient (52, 53) there have been no issues reported among face transplant recipients. Four of 34 patients were blind (12%); initially blindness has been considered as a relative contraindication, but reports show results equal or better than in non-blind patients (39, 54). Blind patients even may psychologically profit more of FT knowing that they have a normal facial appearance and are not stared at in a crowd.

The overall good outcomes are probably the result of extensive preoperative psychiatric screening of these patients; they have to be very well motivated and compliant. Because of the complexity of the procedure, still not fully known risks and benefits (due to relatively short follow-up), the most important decision is the selection of the candidate. Additionally, extensive and long-term follow-up by a specialized multidisciplinary team is mandatory for good outcomes.

Conclusion

CTA is a relatively new technique that represents the ultimate fusion of principles of microsurgical reconstructive surgery and organ transplantation. It is a life changing procedure, unlike solid organ transplantation and strives for reconstructing complex defects using the principle of plastic surgery pioneer Sir Harold Gillies replacing "like with like". Facial transplantation is an option for patients with complex, devastating and otherwise non-reconstructable facial deformities to restore appearance and overall well-being in a single operation. In the past 9,5 years, 34 patients have undergone this procedure, but as in both world wars, it is probable that numerous soldiers wounded in the recent wars could benefit from this operation. Depletional induction therapy and a standard triple drug immunosuppressive therapy have been used with good functional results and overall favorable graft survival. All cases had at least one acute rejection period successfully treated, no cases of chronic rejection have been reported so far. Opportunistic infection is the most common complication encountered postoperatively, but the adverse effects are less than in patients with solid organ transplants as most of them are otherwise healthy with no co-morbidities. Satisfaction rate is high despite the fact that patients have to follow the immunosuppressive regimen, an intense rehabilitation program and require strict follow-up by a multidisciplinary team. All these data have accomplished that facial CTA has been accepted as alternative therapy in reconstructive surgery. The key to success in this procedure lies in the selection of the appropriate patient who is stable, well motivated and therapy compliant. Thorough screening by a multidisciplinary team, well prepared surgical approach and intensive, early rehabilitation are all crucial factors for a safe and rapid recovery.

Surgical team	Date	Location	Recipient Age/Sex	Allograft	Cause	Extent of Defect
Devauchelle et al.	November 2005	Amiens, France	38, F	Partial	Dog bite	Cheek, nose, lips, chin
Guo et al.	April 2006	Xi'an, China	30, M	Partial	Bear bite Died 27 months post surgery (2008)	Cheek, nose, upper lip, maxilla, orbital wall, zygoma
Lantieri et al.	January 2007	Paris, France	29, M	Partial	Neurofibromatosis	Forehead, brows, eyelids, nose, lips, cheeks, chin
Siemionow et al.	December 2008	Cleveland, USA	45, F	Partial	Ballistic trauma	Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla
Lantieri et al.	March 2009	Paris, France	27, M	Partial	Ballistic trauma	Nose, lips, maxilla, mandible
Lantieri et al.	April 2009	Paris, France	37, M	Full 2 forearms	Third degree burn Died two months post surgery (2009)	Forehead, scalp, nose, eyelids, ears, cheek
Pomahac et al.	April 2009	Boston, USA	59, M	Partial	Electrical burn	Lower eyelid, cheek, nose, lips, maxilla, zygoma
Cavadas et al.	August 2009	Valencia, Spain	42, M	Partial	Cancer Died 4 years post surgery (2013)	Lower lip, tongue, floor of mouth, mandible
Lantieri et al.	August 2009	Paris, France	33, M	Partial	Ballistic trauma	Cheek, nose, lips, maxilla, mandible
Devauchelle et al.	November 2009	Amiens, France	27, M	Partial	Ballistic trauma	Nose, lips, mandible
Gomez Cia et al.	January 2010	Seville, Spain	35, M	Partial	Neurofibromatosis	Cheek, lips, chin, mandible
Barret et al.	March 2010	Barcelona,Spain	31, M	Full	Ballistic trauma	Eyelids, nose, lips, zygoma, maxilla, mandible
Lantieri et al.	June 2010	Paris, France	35, M	Full	Neurofibromatosis	Eyelids, ears, nose, lips, oral mucosa
Pomahac et al.	March 2011	Boston, USA	25, M	Full	Electrical burn	Forehead, eyelids, left eye, nose, cheek, lips
Pomahac et al.	April 2011	Boston, USA	30, M	Full	Electrical burn	Forehead, eyelids, nose, cheek, lips

Surgical team	Date	Location	Recipient Age/Sex	Allograft	Cause	Extent of Defect
Lantieri et al.	April 2011	Paris, France	45, M	Partial	Ballistic trauma	Nose, mandible, maxilla
Lantieri et al.	April 2011	Paris, France	41, M	Partial	Ballistic trauma Died 4 years post surgery (2015)	Nose, mandible, maxilla
Pomahac et al.	May 2011	Boston, USA	57, F	Full	Animal attack	Forehead, eyelids, eyes, nose, lips, maxilla, mandible
Blondeel et al.	December 2011	Gent, Belgium	54, M	Partial	Ballistic trauma	Left cheek, lips, left lower eyelid, eyes, nose, left zygoma, maxilla, left hemi mandible
Ozkan et al.	January 2012	Antalya, Turkey	19, M	Full	Burn	Face skin only
Nasir et al	February 2012	Ankara, Turkey	25, M	Full	Burn	Face skin only
Ozmen et al	March 2012	Ankara, Turkey	20, F	Partial	Ballistic trauma	Nose, upper lip, chin, maxilla
Rodriguez et al	March 2012	Baltimore, USA	37, M	Full	Ballistic trauma	Forehead, eyelids, nose, cheek, lips, zygoma, maxilla, mandible
Ozkan et al	May 2012	Antalya, Turkey	27, M	Full	Burn	Face, ears
Devauchelle et al	September 2012	Amiens, France	F	Information not available	Vascular tumor	Information not available
Pomahac et al	February 2013	Boston, USA	44, F	Full	Chemical burn	Nose, eyelids, lips, forehead, cheek, ears, eyes
Maciejewski et al	May 2013	Gliwice, Poland	33, M	Partial	Industrial accident	Nose, lips, eyelids, chin, maxilla, cheek
Ozkan et al	July 2013	Antalya, Turkey	27, M	Full	Ballistic trauma	Forehead, eyelids, left eye, nose, cheek, maxilla, mandible
Ozkan et al	August 2013	Antalya, Turkey	54, M	Full	Ballistic trauma died 1 year post surgery (2014)	Scalp, eyelids, mandible, maxilla, nose, hemitongue
Ozkan et al	Dec 2013	Antalya, Turkey	22, M	Partial	Ballistic trauma	Nose, upper lip, maxilla

Surgical team	Date	Location	Recipient Age/Sex	Allograft	Cause	Extent of Defect
Maciejewski et al	Dec 2013	Gliwice, Poland	26, F	Full	Neurofibromatosis	Forehead, brows, eyelids, nose, lips, cheeks, chin
Pomahac et al	March 2014	Boston, USA	35, M	Partial	Ballistic trauma	Mandible, nose and midface
Siemionow et al	Sept 2014	Cleveland, USA	M age unknown	Full	Unknown trauma	90% of face: 2/3 scalp, forehead, eyelids and sockets, nose, upper cheeks, upper jaw with teeth
Pomahac et al	Oct 2014	Boston, USA	31, M	Partial	Ballistic	Lower 2/3rd of the face

Table 1.1: Overview of the 34 face transplants performed worldwide with patient data; M = male, F = female.

Surgical team	Date	Induction	Maintenance	Acute rejection	Rescue therapy	Infectious complications
Devauchelle et al.	November 2005	ATG x10 d hematopoietic stem-cell transplantion MMF 2g/d TAC 10-15ng/ml Prednisone taper	TAC (10-15ng/ml) MMF 2g/d Prednisone taper ECP	pod 18 pod 214	pulse dose steroids pulse dose steroids	pod 18 *Candida* stomatitis pod 185 Labial HSV1 mo 7-8 molluscum contagiosum mo 50 HPV cervical carcinoma in situ
Guo et al.	April 2006	hIL-2AB 50mg TAC (25ng/ml) MMF 2 x 0,5g Methylprednisolone 1g X-ray graft (4Gy)	TAC (10-15ng/ml) MMF Prednisone	mo 3 mo 5 mo 7 mo 17	pulse dose steroids	Died 27 months post surgery (2008)
Lantieri et al.	January 2007	ATG 1mg/kg x 10d TAC (10-13ng/ml) MMF 2g/d Prednisone taper	TAC (8-10ng/ml) MMF Prednisone ECP 2x/w for 1 mo ECP 1x/mo for 3 mo	pod 28 pod 64	pulse dose steroids pulse dose steroids + ATG	pod 65 CMV viremia donor syphilis
Siemionow et al.	December 2008	ATG 1,2mg/kg/d x 9d Methylprednisolone 1g	TAC (10-15ng/ml) MMF Prednisone	pod 47	single dose IV corticosteroids	mo 11 CMV viremia mo 13 *C. difficile* and *Aeromonas* diarrhea
Lantieri et al.	March 2009	ATG 1mg/kg x 10d TAC (10-13ng/ml) MMF 2g/d Prednisone taper	TAC (8-10ng/ml) MMF Prednisone ECP 2x/w for 1 mo ECP 1x/mo for 3 mo	pod 0	steroid bolus	pod 2 *Pseudomonas* pneumonia
Lantieri et al.	April 2009	ATG 1mg/kg x 10d TAC (10-13ng/ml) MMF 2g/d Prednisone taper	TAC (8-10ng/ml) MMF Prednisone ECP 2x/w for 1 mo ECP 1x/mo for 3 mo	no rejection	-	multi-drug resistant *Pseudomonas* infection of grafts Died pod 65 (2009)

Surgical team	Date	Induction	Maintenance	Acute rejection	Rescue therapy	Infectious complications
Pomahac et al.	April 2009	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	mo 34 mo 56	pulse dose steroids pulse dose steroids	pod 10 recurrent HCV pod 96 parotitis, recurrent at 2 and 3 yrs pod 460 CMV syndrome pod 187 *Trichophyton rubrum* granuloma
Cavadas et al.	August 2009	Basiliximab	TAC MMF corticosteroids (HIV + patient under HAART)	pod 14 pod 350	pulse dose steroids pulse dose steroids	mo 11 pseudosarcomatous spindle-cell tumor SCC cancer recurrence Died 4 years postop (2013)
Lantieri et al.	August 2009	ATG 1mg/kg x 10d TAC (10-13ng/ml) MMF 2g/d Prednisone taper	TAC (8-10ng/ml) MMF Prednisone ECP 2x/w for 1 mo ECP 1x/mo for 3 mo	pod 5	X	pod 3-10 labial HSV1
Devauchelle et al.	November 2009	ATG x 10d MMF 2g/d TAC 10-15ng/ml Prednisone taper	TAC Prednisone	pod 41 pod 103 mo 6 mo16 mo18	X	mo 4 B-cell lymphoma (R/rituximab)
Gomez Cia et al.	January 2010	Basiliximab 2 x 20 mg TAC Prednisone taper	TAC MMF steroids	pod 28	pulse dose steroids oral TAC adjustment and topical TAC	wk 3 and 7 CMV viremia first 47 d *Acinetobacter baumanii* surgical site infection and tracheobronchitis and *Enterobacter cloacae* bacteremia
Barret et al.	March 2010	ATG 1 x 2mg/kg Prednisone 1 x 1mg/kg		pod 28	pulse dose steroids	not reported
Pomahac et al.	March 2011	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	mo 22	pulse dose steroids	pod 8 *Pseudomonas Aeruginosa* at surgical site pod 8 *Candida albicans* at surgical site pod 26 sialocele superinfected with *Peptococcus saccarolyticus*

Surgical team	Date	Induction	Maintenance	Acute rejection	Rescue therapy	Infectious complications
Pomahac et al.	April 2011	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	pod 20 mo 17 mo 34	pulse dose steroids pulse dose steroids	pod 1 *Haemophilus influenza* pneumonia pod 90 polymicrobial bacteremia (*E.cloacae,a-*hemolytic streptococcus, coagulase negative staphylococcus) pod 210 CMV gastritis pod 240 HSV reactivation chin
Pomahac et al.	May 2011	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	pod 54 mo 17 mo 30	pulse dose steroids pulse dose steroids	pod 5 loss of hand allografts pod 1 pneumonia with *Serratia marcescens, Proteus mirabilis* and *Pseudomonas aeruginosa* pod 28 zygomatic fluid collection *Enterococcus* vancomycin-resistant pod 90 *Clostridium difficile*-associated diarrhea pod 270 presumed viral gastroenteritis pod 330 palpebral conjunctivitis
Blondeel et al.	December 2011	ATG 4mg/kg X 7d TAC (10-15ng/ml) MMF 2g/d Methylprednisolone taper	TAC (10-15ng/ml) MMF Prednisone	mo 4	pulse dose steroids + IVIG	wk 16 abscess osteosynthesis plate with *Aspergillus fumigatus* mo 4 sinusitis with *Pseudomonas aeruginosa* mo 5 pulmonary *Aspergillus fumigatus* mo 6 asymptomatic CMV viremia mo 11 relapse of pulmonary *Aspergillus fumigatus*, superinfection pneumonia with *Pseudomonas aeruginosa* mo 31 relapse of pulmonary *Aspergillus fumigatus*
Rodriguez et al	March 2012	Alemtuzumab 30 mg Methylprednisolone 500 mg	TAC (10-15ng/ml) MMF Prednisone	pod 51 pod 402 pod 710	pulse dose steroids	X

Surgical team	Date	Induction	Maintenance	Acute rejection	Rescue therapy	Infectious complications
Pomahac et al	February 2013	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d preparation with IVIG and TPE (highly sensitized patient PRA score >85%	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	pod 5 pod 19	steroid bolus, ATG, plasmapheresis, IVIG, eculizumab, bortezomib, alemtuzumab	mo 11 fungal nail infection
Pomahac et al	2014	MMF 1 x 1 g Methylprednisolone 1,5 g/d x 3 d ATG 1,5mg/kg/d x 4d	TAC (10-15ng/ml) MMF 2g/d Prednisone taper over 60-100d	mo 3	pulse dose steroids	X

Table 1.2: Overview of immunosuppressive regimen/rejection/infectious complications of reported face transplants performed worldwide.

X = not reported, ATG = anti-thymocyte globulin, MMF = mycophenolate mofetil, TAC = tacrolimus, ECP = extracorporal photopheresis, hIL-2AB = human interleukin 2 antibody, HIV = human immunodeficiency virus, HAART = highly active antiretroviral therapy, IVIG = intravenous immunoglobulins, CMV = Cytomegalovirus, HSV = herpex simplex virus, HPV = human papilloma virus, d = days, pod = postoperative day, mo = month, wk = week, TPE = total plasma exchange, PRA = panel of reactive antibodies.

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CHAPTER 2

Establishing a face transplant program at Ghent University Hospital, Belgium

Abstract:

Composite tissue allotransplantation (CTA) has evolved from the experience of solid organ transplantation and represents a promising surgical option to restore the form and function of missing or severely damaged structures such as hands, trachea, abdominal wall and face.

This article describes the process of establishing a facial CTA program at Ghent University Hospital, Belgium. The whole process took about 2 years; in December 2011 the first successful facial CTA was performed. The purpose of the program is to perform 5 face transplantations included in the protocol. On the long term the program will be extended to other types of CTA in collaboration with other departments of the hospital and other CTA centers in Europe within the setting of Eurotransplant.

Key Words:

Composite tissue allotransplantation; Face transplant; Multidisciplinary team approach.

Introduction

Composite tissue allotransplantation (CTA) represents the fusion of solid organ transplantation and microsurgical reconstructive plastic surgery. It is the ultimate option to reconstruct defects or missing structures respecting the replacing "like with like" principle and indicated for restoration of missing defects or body parts in the most disfigured patients that are otherwise impossible to reconstruct such as hand, trachea, abdominal wall or face.

Regarding facial reconstruction, surgeons often are frustrated by the suboptimal results, especially when dealing with specialized central facial tissue such as nose, lips and eyelids. The anatomy of the central part of the face is so unique and able to perform vital functions including breathing, mastication, swallowing, and other social functions such as speech and non-verbal communication. At this very moment, conventional plastic surgical methods are unable to reconstitute these functions.

The realization that there is a need for better facial reconstruction techniques represents a starting point that has led to the establishment of CTA centers in France and USA (1-5). Face transplantation (FT) has opened new horizons in facial reconstructive surgery and given hope to patients with difficult and severely disfiguring defects. The extent (partial or full face transplant) and type of tissues (bone, muscle and soft tissue) transplanted are unique and specific to each patient's deformities resulting in a highly variable surgical planning and procedure.

In the Benelux, no such center existed until 2010; as international leading and known plastic and reconstructive department and given the long history of our experienced transplant surgery department, we felt the need to establish a FT center. At the time when we started, only 10 face transplants had been performed worldwide: 6 in France, 1 in China, 1 in Spain and 2 in the USA.

Setting up the program

A successful face transplant center needs a valid research protocol, a solid infrastructure, an expert multidisciplinary team and adequate resources and funding. Setting up a program usually takes between 1 to 3 years (1 - 7). The time line as experienced our hospital can be found in table 2.1.

The program started by writing a research protocol for facial CTA by the team leader Prof. Dr. Phillip Blondeel, an international known plastic and reconstructive surgeon with significant experience in microsurgery, interest in clinical research and an outmost dedication to the project. He supervised every single step of the process, from the initial protocol submission to the long-term postoperative care.

Other groups have defined the responsibilities of the team leader as well as how the team should be assembled (core team and other involved disciplines), who should be included and the participation of the various members of the multidisciplinary team in each of the various stages of the face transplant protocol (2, 4, 5). As with any other complex medical problem, a multidisciplinary approach is paramount to the well-being of the patient and the overall success of the program.

Aspects of facial composite tissue allotransplantation

When setting up guidelines for a CTA program, different aspects of facial transplantation are encountered, such as the protocol, patient selection, donor selection, procurement, costs etc.

In the following sections, all aspects will be discussed individually.

The protocol

In the protocol, focus was put on the Ethical Guidelines for Composite Tissue Allotransplantation as formulated by the Louisville USA group in 2004 (8).

1. *Scientific background in the innovation*

At the time of proposing the protocol to the Institutional Review Board (IRB) /Ethics Committee, 10 face transplants already had been performed worldwide, indicating that this type of surgery was no longer in an experimental phase.

2. *Skill and experience of the team*

A core team was assembled consisting of experienced reconstructive microsurgeons, head and neck/craniomaxillofacial surgeons and transplant surgeons. Other experienced members of necessary medical and paramedical disciplines as indicated by the guidelines of other CTA teams were included.

3. *Open display and public and professional discussion and evaluation*

The Ghent Ethics Committee represents the general public and professional society. The protocol for face transplantation was extensively and elaborately discussed within the Committee before final approval was given. The surgical procedure is linked to an array of complicated ethical issues inherent to the surgery itself, personal identity, patient's quality of life, implementation of medical resources and a lifelong postoperative treatment and care. FT patients require lifelong immunosuppression with inherent complications for a condition that is in se not physiologically life threatening (in contrast to cardiac or renal transplantation).

4. *Ethical climate of the institution*

The innovation is not being performed for purposes of institutional prestige or professional recognition; the long-term goal is to establish a unit for all types of CTA (not only face) in our hospital. It involves a long-term commitment of the multidisciplinary team and the hospital to offer this innovative therapy as new treatment option to severely facial disfigured patients.

5. *Sufficient research performed*

For specific preparation, cadaver sessions were performed to practice face transplantations. These sessions allowed the team to write scripts including every detail of the actual transplantation, not only for the surgeons but also for the scrub nurses and to foresee and overcome practical issues (such as suitable instrumentation, setting up operating room). The sessions also allowed the surgeons to deal with timing issues: how long it would take to perform face transplantation with one team harvesting the allograft and the other team creating the defect in the recipient? In case the recipient is known, specific mock transplantations can be practiced to ensure all details are complete. Additionally, the anaplastologists of the team practiced the technique for perfecting the fabrication of the death mask. This step is an ethical requirement and important for restoration of the face of the donor preserving its dignity. Otherwise families and organ procurement agencies will possibly not cooperate for future face transplantations (9).

6. *Informed and willing subjects*

There exist informed subjects who, deeming the procedure beneficial, want to undergo it. Potential candidates should sign informed consent and accept advantages and disadvantages of the procedure. Opting out is possible at every stage. The candidate and family should be informed about the visual aspect of the new face; that it will not resemble the donor. This knowledge is based on experience with previous transplants and other research (10, 11). Specific written permission has to be obtained of the donor family for procurement of the facial allograft. Anonymity should absolutely be guaranteed. The dignity of the donor has to be restored with a facial mask (see above).

7. *An important existing need for the treatment*

There exist many other potential subjects who could, in the future, benefit from this procedure if it proves to be successful.

8. *Regulatory approval*

The procedure has been subjected to the established regulatory scrutiny and reviews, including approval by the relevant Institutional Review Board for the Protection of Human Subjects (IRB).

The goals are to include 5 patients for studying feasibility and reliability of facial transplantation. The results of this (life changing but not life saving) procedure and the effects of the immunosuppressive therapy will be evaluated and scientifically tested to measure the impact on the overall quality of life of the patient (table 2.2).

<u>Collaboration with the organ processing donor organization</u>

The face should be considered as an organ (see Chapter 1). In Europe, Eurotransplant was created in 1967 and represents a non-profit organization facilitating patient-oriented allocation and cross-border transparent exchange of deceased donor organs. The total population of the eight Eurotransplant member states numbers almost 135 million people and accounts for 1,601 donor hospitals and 72 transplant centers. This cooperation allows for a much larger pool of donor organs and, by using a central waiting list, shortens waiting time. Right now, 16.000 patients are waiting for an organ donation in these 8 countries and Eurotransplant yearly allocates over 7,000 organs (12). Our first patient was enlisted in Eurotransplant for face transplantation (first case worldwide); other candidates will also be registered as such.

Patient selection

The candidate evaluation involves every single member of the team who has to give approval. In addition advice of other experienced centers will be asked to discuss the indication for face transplantation.

Special care must be taken to explain to the patient and the family the complexity of the surgery, the possible complications, the side effects of lifelong immunosuppression and the long-term commitment/compliance needed for such an intervention. He must be fully psychiatrically assessed not only by the involved team members but also by an independent physician and psychologist who will decide if the patient has realistic expectations and is mentally, emotionally, cognitively capable to undergo such a stressing and radical treatment involving important changes in terms of personal identity. Social workers will meet with the patient's relatives prior to the surgery and confirm that his social environment is appropriate. A patient's advocate needs to be put in place to defend the patient's best interests all along. Although possible, it does not necessarily have to be a family member.

A full preoperative work up of the candidate has to be performed as described in details by Bueno (4).

In our protocol, inclusion criteria are:

- age between 18 and 65 years
- full thickness defect of central part of the face, otherwise non-reconstructable (post traumatic or congenital)
- availability of other reconstructive options in case of transplant failure
- psychological stable
- normal preoperative work up

Absolute exclusion criteria are:

- active smokers
- medical unstable condition
- oncologic medical history
- pregnant or lactating women
- serious active and chronic infections (eg. HIV)
- toxicomania
- psychiatric unstable patients

Donor selection

The criteria for donor inclusion are variable between different CTA groups (13). In our institute, brain-death heart-beating donation was selected; the donor has to match the recipient in age, sex, phototype according to Fitzpatrick (14) and anthropomorphic features. The group of Boston has estimated the ideal donor's age between 20 years younger and 10 years older than the recipient also taking into consideration the skin texture (11). Additional criteria are ABO compability, negative crossmatch and general guidelines of Eurotransplant concerning infectious diseases and history of carcinoma. If possible, HLA compatibility is preferred, although successful transplants have been performed with complete mismatch between donor and recipient (15). The Ghent Ethics Committee desired that the donor procedure took place in our own hospital or an affiliated hospital in Ghent. This was mainly for logistic reasons and for allograft ischaemia time considerations (less than 4 hours).

Organ procurement and donor surgery

As soon as brain-death status of the donor is confirmed and he/she has not objected to donorship, the transplant coordinator of the team and treating physician will discuss donation of the face with the family. Specific written informed consent for donation of the facial allograft has to be obtained. If the family gives consent, the face transplant team leader will examine the patient to evaluate if the face of the donor meets the requirements of the potential recipient. If so, the donor will be fully screened including radiographic examination of the face. If no contraindications exist and the transplant can proceed, the team leader will notify and mobilize the surgical transplant team. Specific flow chart, timetables and scripts have been designed and written for the involved surgeons, anesthesiologists and paramedic personnel.

Primary concern is the safe allocation, procurement and recovery of "life-saving organs". The facial allograft is recovered prior to the solid organs, unless the donor becomes unstable, in which case life-saving organs are given priority (4, 15 - 17) although some teams have described simultaneous procurement (6, 18). After procurement, the face is placed on a custom-made template and flushed during 30 min. with standard histidine-tryptophan-ketoglutarate solution to protect the tissues during hypothermia and transportation. An important step in the surgical protocol is the restoration of the face of the donor. The anaplastologists, members of the multidisciplinary team, will fabricate a silicon death mask, which will guarantee a very natural result, practically indistinguishable from real. This approach will allow the family to greet the deceased in a respectful and serene atmosphere.

Donor family

As mentioned above, the treating physician/intensivist and transplant coordinator will discuss the possibility of donation of the face with the family. For this difficult and delicate issue, our coordinators have followed specific training in experienced centers. Studies have proved that the face of the recipient will not be same as the donor (10, 11). The family has to be reassured that the face of their beloved one will not be recognizable in the transplanted patient and that anonymity is absolutely guaranteed. They should be informed that the face of the donor will be restored with a mask after procurement to preserve dignity and allowing open casket funeral. Counseling and support is offered by an experienced psychologist and the transplant coordinator. This support will continue after the transplantation as long as wanted and needed by the family. Only when the family is fully cooperative and willing to participate with the multidisciplinary team before, during and after the transplantation, the procedure of facial procurement will take place.

Facial transplantation

Ideally facial allograft procurement and preparation of the recipient start at the same time by two surgical teams working in 2 adjacent operating theatres. A sentinelflap will be taken from the forearm of the donor and transplanted to the recipient. This flap serves as a monitoring island to assess rejection and is easy accessible for skin biopsies (3). During the transplantation, the anaplastologists fabricate the mask to reconstitute the face of the donor after graft procurement (see above). The transplant coordinator communicates between the 2 rooms and keeps the teams for subsequent organ procurement posted. After facial allograft procurement, the actual transplantation in the recipient begins with the microsurgical anastomoses and the other teams continue with organ procurement in the donor. The anaplastologists finish the mask, allowing preservation of the dignity of the donor and the family.

Immunosuppressive therapy

The immunosuppression is coordinated by the immunologist/nephrologist of the team. In our hospital, there is a long history of experience with solid organ transplantation. Induction with anti-thymocyte globulin and steroid taper and maintenance triple therapy with tacrolimus, mycophenolate mofetil and prednisone are used (table 2.3). The therapy must be closely monitored for the duration of the patient's life. Over-immunosuppression (during induction or treatment of rejection) can lead to undesirable side effects such as infections, osteoporosis, nephrotoxicity. Under-treatment leads to rejection. Over time, the goal is to gradually reduce the doses, while avoiding allograft rejection. The Banff CTA 2007 Classification for Cell-Mediated Acute Rejection (19) is used. When rejection is suspected, the diagnosis has to be made by combining the clinical situation and results of skin/mucosa biopsies. The acute/active skin rejection system is divided in five grades, based on intensity and localization of infiltrates (table 2.4). For acute rejection high-dose steroids and optimization of maintenance immunosuppression are used. Skin biopsies are performed weekly during the first month after transplantation from the face and sentinel flap and on indication thereafter, if rejection is suspected.

Postoperative care

The patient is transferred to the Burn Intensive Care Unit of our hospital where he will stay until discharge. This department is specialized both in high care of burn patients and in monitoring the vascular status of flaps (in this case the allograft). Besides this, this unit offers isolated rooms, important for the prevention of infections in the acute phase and protection from undue media attention (see below).

Clinical monitoring of the patient and assessment of the graft is provided by the team leader and surgical members of the team. The immunologist/nephrologist coordinates the immunosuppressive, anti-microbial, anti-viral and anti-fungal

therapy and closely follows the patients for rejection, infectious complications and immunotherapy related side-effects.
Rehabilitation therapy consisting of facial physical and speech therapy is started as soon as possible and is mandatory to obtain maximum motor recovery; the protocol is tailored for each patient. Frequent psychiatric and psychological counseling and assessment is of utmost importance for the patient and the family.

Media

By the vivid imagination of many people, this type of surgery is often regarded as innovative and spectacular. It has been difficult dealing with the press in a correct way in order to give them appropriate and realistic information. Even more cumbersome are the measures taken to ensure anonymity of the donor and recipient; they need to be protected as well as their families. A protocol for dealing with the media has been prepared in collaboration with the department of press and communication of the hospital. All directly and indirectly involved team members and collaborators have been instructed to keep a strict professional attitude and silence to outsiders.

Costs

Facial transplantation and patient postoperative care including immunosuppressive therapy are very costly. Initial high dose and later lower maintenance dose immunosuppressive drugs weigh the most in the total budget. Other groups have performed financial analyses and the costs are different for each country depending on the healthcare system (20, 21).
The decision to establish a face transplant program in a university hospital results in a long-term commitment of the multidisciplinary team and the hospital board to offer this innovative therapy as new treatment option to severely facial disfigured patients. As this procedure was seen as experimental surgery by the Ethics Committee and the insurance company, no costs were charged to the patient or his family. Certain costs, such as the hospital stay and the immunosuppressive therapy were sub-totally reimbursed by the national health care insurance. All physicians involved with the facial transplant program did not charge honorary fees to the patient. The final cost of the surgical procedure

was 11.000 euros; the total cost for the coming 10 years including the immunosuppressive therapy is calculated around 120.000 euros.

Conclusions

We described our experience and the issues encountered with setting up a program for facial transplantation. A well-led multidisciplinary team composed of experts from diverse professional backgrounds and in which every member has a clearly defined role is the key to success to handle the unique set of problems and challenges of facial disfigured patients in whom transplantation offers a new future and hope.

Funding: none

Conflicts of interest: none declared

Ethical approval was obtained by the Ethics Committee of the Ghent University Hospital in accordance with the principles of the Declaration of Helsinki (file nr. 2001/022)

Date	Event
09-04-2009:	Start administrative process (protocol)
12-03-2010:	Start cadaver dissections
19-07-2010:	Ethics Committee "no objections"
27-12-2010:	Recruitment first possible candidate
early 2011:	Approval medical board and CEO hospital
11-04-2011:	Official approval Ethics Committee
29-04-2011:	Signing of informed consent form by first recipient
16-06-2011:	First registration in Eurotransplant (for face transplantation)
30-12-2011:	First Belgian face transplant

Table 2.1: Summary of dates and events in process of setting up a FT transplant program in the Ghent University Hospital, Belgium.

Assessment	preop	1wk	2wk	1mo	3mo	6mo	12mo	18mo	24mo	36mo	60mo
Clinical outcome											
- standard photographs	X	X	X	X	X	X	X	X	X	X	X
- videotaping	X				X		X		X	X	X
Speech											
- intelligibility/ acceptability/voice/ resonance/articulation/ oromyofunctional behavior/facial disabililty index	X	X	X			X	X		X	X	X
Motor recovery											
- electromyography face	X				X		X		X	X	X
- CNV during sentence completion task	X			X		X	X		X	X	X
- sequential electromyography lips	X			X		X	X		X	X	X
Sensory recovery											
- Semmes-Weinstein monofilament testing	X				X	X	X		X	X	X
Psychiatric outcome see below*	X							X		X	X

CNV = contingent negative variation
*Beck Depression Inventory II, the Spielberger State Anxiety Inventory, the Beck Hopelessness Scale, the Utrecht Coping List, the Temperament and Character Inventory, the Dutch Resilience Scale, the Family Assessment Device, the Dyadic Adjustment Scale, the Quality of Relationships Inventory, the Illness Cognition Questionnaire, the 36-item Short Form Health Survey and the MINI psychiatric interview.

Table 2.2: Overview of assessment methods and timing.

Induction	Maintenance
anti-thymocyte globulin: 4mg/kg/d day 0 - 6 **tacrolimus:** 0,2 mg/kg/d **mycophenolate mofetil:** 1 gr BID day 0 - 10 **methylprednisolone:** 500mg IV at incision (day 0) 250 mg day 1 125 mg day 2	**tacrolimus:** 0,2 mg/kg/d (targeted trough concentration 10-15 ng/ml during first 3 months; tapering to 0,5mg BID targeted trough concentration 4-5 ng/ml) **mycophenolate mofetil**: 1 gr BID tapering to 500 mg BID **methylprednisolone** 40mg/d from day3, tapering to 8mg/d at end of month 3; further tapering to 4 mg/d

Table 2.3: Immunosuppressive regimen used in the protocol; BID = bidaily, IV = intravenous.

Grade 0:	No or rare inflammatory infiltrates.
Grade I:	Mild. Mild perivascular infiltration. No involvement of the overlying epidermis.
Grade II:	Moderate. Moderate-to-severe perivascular inflammation with or without mild epidermal and/or adnexal involvement (limited to spongiosis and exocytosis). No epidermal dyskeratosis or apoptosis.
Grade III:	Severe. Dense inflammation and epidermal involvement with epithelial apoptosis, dyskeratosis and/or keratinolysis.
Grade IV:	Necrotizing acute rejection. Frank necrosis or epidermis or other skin structures.

Table 2.4: The Banff 2007 working classification of skin-containing composite tissue allograft pathology.

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CHAPTER 3

Aims of the thesis

List of publications

Aims of the thesis

The aims of this doctoral thesis are to provide evidence for the following hypotheses:

1. In well-selected cases of patients with large central facial defects, facial transplantation offers the only possibility to restore anatomy, aesthetics, vital and social functions in a single procedure as it replaces "like with like" which is impossible with conventional surgical techniques
2. Three dimensional modeling and digital planning are valuable tools in planning facial composite tissue allografting to improve accuracy and speed of the procedure.
3. Meticulous pre-operative planning and continuous, long-term follow-up by a large multidisciplinary team are essential to build a facial composite tissue allotransplantation (CTA) program.
4. Anaplastology is indispensable when performing facial transplantation for reconstitution of the donor and as adjunctive tool for reconstitution of difficult to reconstruct facial structures in the recipient.
5. From a psychological point of view, facial transplantation is a life changing procedure, as it improves quality of life and overall well-being of severely facial disfigured patients.
6. The keys to success in facial transplantation lie in the selection of the appropriate patient who is stable, well motivated and therapy compliant and definition of the appropriate indication of this procedure.
7. Blindness is not a contra-indication for facial transplantation.
8. The long-term goals of an established CTA center include intensive collaboration between departments of the leading hospital and communication between the different CTA centers in Europe within the setting of Eurotransplant.

List of publications

This doctoral thesis is based on the following articles published or submitted in international peer-reviewed journals:

1. Roche Nathalie A, Blondeel Phillip N, Van Lierde Kristiane M, Vermeersch Hubert F. Facial transplantation: history and update. Acta Chir Belg 2015;115(2):99-103.
   A1, impactfactor 0,44/Q4

2. Roche NA, Vermeersch HF, Stillaert FB, Peters KT, De Cubber J, Van Lierde K, Rogiers X, Colenbie L, Peeters PC, Lemmens GMD, Blondeel PhN. Complex Facial Reconstruction by Vascularized Composite Allotransplantation: the first Belgian case. J Plast Reconstr Aesthet Surg 2014 doi:10.1016/j.bjps.2014.11.005.
   A1, impactfactor 1,474/Q2

3. Van Lierde K*, Roche N*, De Letter M, Corthals P, Stillaert F, Vermeersch H, Blondeel Ph. Speech characteristics one year after first Belgian facial transplantation. Laryngoscope. 2014 Sep;124(9):2021-7.
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   A1, impactfactor 1,979/Q1

4. Longitudinal progress of overall intelligibility, voice, resonance, articulation and oromyofunctional behavior during the first 21 months after Belgian facial transplantation. Van Lierde KM, De Letter M, Vermeersch H, Roche N, Stillaert F, Lemmens G, Peeters P, Rogiers X, Blondeel Ph, Corthals P. J Commun Dis 2014 doi:10.1016/j.comdis.2014.09.001.
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patient: Psychological, marital and family outcomes at 15 months follow-up. Psychosomatics 2014 doi:10.1016/j.psym.2014.05.002.
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A1, impactfactor 3,309/Q1

7. Roche NA*, Blondeel PhN*, Vermeersch HF, Peeters PC, Lemmens GMD, De Cubber J, De Letter M and Van Lierde KM. Long-term multifunctional outcome and risks of face vascularized composite allotransplantation. J Craniofac Surg 2015 (submitted).
*equal contribution
A1, impactfactor 0,676/Q4

To the patient, any operation is momentous.

Joseph Murray

Part 2

Results

CHAPTER 4

Complex facial reconstruction by vascularized composite allotransplantation: the first Belgian case

Based on:

Nathalie A. Roche, Hubert F. Vermeersch, Filip B. Stillaert, Kevin T. Peters, Jan De Cubber, Kristiane Van Lierde, Xavier Rogiers, Luc Colenbie, Patrick C. Peeters, Gilbert M.D. Lemmens and Phillip N. Blondeel. Complex facial reconstruction by vascularized composite allotransplantation; the first Belgian case. *J Plast Reconstr Aesthet Surg 2014 doi:10.1016/j.bjps.2014.11.005.*

Abstract:

Introduction: Complex injuries of the central part of the face are difficult to reconstruct with current plastic surgery methods. The ultimate one-staged approach to restore anatomy and vital facial functions is to perform a vascularized composite allotransplantation (VCA).

Methods: A 54-year-old man suffered from a high-energy ballistic injury, resulting in a large central facial defect. A temporarily reconstruction was performed with a free plicated anterolateral thigh (ALT) flap. Considering the goal to optimally restore function and aesthetics, VCA was considered as option for facial reconstruction. Multidisciplinary team approach, digital planning and cadaver sessions preceded the transplantation.

Results: A digitally planned facial VCA was performed consisting of bilateral maxillae, hard palate, part of the left mandible together with the soft tissues of the lower 2/3rd of the face. Due to the meticulous preparations, minimal adjustments were necessary to achieve good fitting in the recipient. At week 15, a grade IV rejection was successfully treated; sensory and motor recovery was noted to occur from the 4th postoperative month. Several serious infectious and medical problems have occurred until 13 months postoperatively, after that the clinical situation has remained stable. Two years postoperatively, the patient and his family are very satisfied with the overall outcome and social reintegration in the community is successful.

Conclusion: The first face transplant in Belgium (#19 worldwide) was successful because of a meticulous 3-year preparation by a large multidisciplinary team. In our experience, preparatory cadaver dissections and 3D CT-modeling were valuable tools for an optimal intra-operative course and good alignment of the bony structures. Continuous long-term multidisciplinary follow up is mandatory for surveillance of the complications associated with the immunosuppressive regime and for functional assessment of the graft.

Key Words

Vascularized composite allotransplantation; Face transplant; 3D CT modeling; Multidisciplinary team approach

Introduction

Vascularized Composite Allotransplantation (VCA) represents the essentiality of reconstructive surgery where defects are repaired with anatomically identical structures (1). After laryngeal transplantations (2,3) and hand- and forearm transplantations in the 90s (4-6), allotransplantation of the face was introduced in 2005 (7). In patients with major defects in the central part of the face due to trauma or congenital defects, it is very difficult to obtain good functional and aesthetic results with traditional pedicled or free autologous flaps especially if the orbicularis oculi and oris muscle functions are lost. In selected cases a VCA of the face offers the only possibility to restore vital facial functions such as breathing, swallowing, mastication, speech and non-verbal communication in a single procedure (7-14).

We report on the first digitally planned face transplantation (#19 worldwide) performed in December 2011 at the Ghent University Hospital, Belgium. The purpose of this manuscript is to share our experience on performing a facial VCA and on the advantages of 3D digital planning and modeling in order to expedite surgery and to achieve optimal functional and aesthetic results as seen in the 2 year follow-up period.

Methods

The patient

A 54-year-old man with a facial ballistic injury was admitted to the emergency department in December 2010. He presented with a major soft tissue defect of the lower two thirds of the face and an extensive loss of facial bony structures, nose, both maxillae, floor of the mouth, left part of the mandible and all dentition (Fig. 4.1 and 4.2). Vision was lost, as both eyes were involved. The majority of the soft palate and a functioning pharynx were intact. The tongue was severely disintegrated but three quarter of the bulk was still present and vascularized. The defects were temporarily approximated after debridement; the facial fractures were stabilized with reconstruction titanium plates where possible. The remaining parts of the mandible were kept in position by a long reconstruction plate. Five days post trauma, a plicated left free anterolateral thigh flap provided coverage of the external skin defect, separation of the oral and nasal cavity, reconstruction of the nasal canal (floor and side walls) and obliteration of the dead space in a one-stage procedure. A tracheostomy was required for breathing, as well as a percutaneous gastrostomy tube for feeding. Swallowing was impossible due to oral incompetence (loss of both maxillae, hard palate, part of the mandible and soft tissues of the cheek) with the risk of aspiration pneumonia; speech was very poor despite intensive postoperative orthophonic treatment, the ability to smell was absent as well as sensation in the left side of the face.

Clinical evaluation and radiological examination, based on CT-scans with 3D-reconstruction, provided an inventory of missing facial bony structures (Fig. 4.3). Deficient soft tissues included the left side of nose with the nasal cartilages, left lower eyelid, a part of the left upper eyelid, left cheek, including the left upper lip and left oral commissure. The 2nd and 3rd branch of the trigeminus nerve were destructed on both sides of the face leading to insensitivity of both cheeks and chin. The destructed muscles included the infra-palpebral left orbicularis oculi, all levators and depressors of the mouth and almost all of the orbicularis oris muscle, leading to oral incompetence. Of the functional areas of the facial nerves, only the zygomaticus major muscle on the right side, the right orbicularis oculi and both frontal muscles were still contracting (see Fig. 4.4 and 4.5 which demonstrate the preoperative appearance of the face).

<u>Preparation</u>

After thorough screening by a multidisciplinary team the patient was considered to be a possible candidate for facial transplantation. Extensive psychological and psychiatric assessment retained no contra-indications for the procedure. At baseline assessment the patient was daily treated with citalopram 40 mg and trazodone 100 mg for a life-time, not current, depressive disorder. Blindness was not considered as an absolute contra-indication. Advice and feedback of other more experienced centers (Paris, France and Cleveland USA) were asked. Final approval for the procedure was obtained from the Ethics Committee and management of the Ghent University Hospital in accordance with the principles of the Declaration of Helsinki.

The patient and his family were well informed about and fully understood the risks and complications of this potentially life-threatening procedure as well as the side effects of the immunosuppressive therapy. In April 2011 a written and video recorded informed consent was obtained; subsequently he was registered as the first candidate for face transplantation on the Eurotransplant waiting list (15).

The lack of radiographic records of our patient before the trauma made it impossible to measure and calculate the dimensions of the missing bones. As experienced during the cadaver dissections, intra-operative adjustments of the transplanted bone by osteotomies, slicing and molding would take an excessive amount of time. Therefore we looked for a way to not only calculate the dimensions of the missing bone but also to pre-operatively determine the position, direction and angle of the planned osteotomies in both the donor and recipient. To approach the ideal skeletal dimensions, we identified a person that morphologically resembled our patient the most, namely his son. Digital subtraction of the cranial 3D CT images of the son and the father showed the appropriate amount and shape of the missing facial bones. In several online meetings between the surgical team and the engineers of Materialise (Synthes ProPlan CMF/SurgiCase Connect, Materialise, Leuven, Belgium) the position and angle of the osteotomies were determined and the repositioning of displaced bony fragments was calculated. The shape, size and position of the osteosynthesis material were also digitally measured and manufactured respectively. Subsequently, specific 3D models of the missing facial bones of the patient were created by 3D printing well as specific jigs in order to guide the osteotomies in both the donor and recipient face during the surgical act (Fig. 4.6 - 4.8). The procedure was rehearsed and practiced with the full surgical team and transplant coordinators at the anatomy lab by performing multiple cadaver dissections.

The donor

A suitable 22-year-old male heart-beating donor with irreversible traumatic brain injury but otherwise healthy was found eight months later. He matched our patient in race, skin complexion and facial morphology. Weight and length of the donor were 85 kg and 1,92m respectively and of the recipient 60 kg and 1,73m. The blood group of the donor was O-positive and that of the recipient was A-negative. Human leucocyte antigen status of the donor was A1 A3 B8 B16 B39 Bw6 DR2 DR16 DR3 DR17 DR51 DR52 and that of the recipient A2 A9 A24 B7 B27 DR2 DR15 DR4. Specific written permission for procurement of the face was obtained from the family in accordance to the Belgian transplant laws and the requirements of Ethics Committee of the hospital.

Anaplastology

At the start of the donor operation, the anaplastology team who trained and prepared during the surgical cadaver sessions took a negative impression of the face of the donor with polydimethylsiloxane elastomer reinforced with synthetic stone in order to produce a silicon "death" mask. The total production time for the facial death mask was estimated between 2-5 hours. The death mask procedure was divided into two phases: proceedings prior (2 hours) and past (3 hours) to removal of the allograft.

After procurement of the facial allograft, the bony defects were restored with plastic dummies produced in advance according to the preoperative planning. The mask was made of 2 layers of silicon colored elastomer; the exact color was defined using silicone pigments and nylon flocking until perfect match with the donor facial skin was achieved. A homogeneous colored sheet of 4mm thickness was produced and placed into the initial silicone impression. By means of liquid silicone manipulation the plastic silicone sheet was modeled onto the impregnated impression. This unvulcanized sheet was reinforced on the inside by a thin layer of fast curing silicone, with an overload of platinum catalyst, until 3cm from the edge. After the supportive silicone layer was vulcanized, both layers were removed from the mold and positioned over the plastic dummies and adapted to the donor skin. The edges of the unvulcanized silicone where thinned out and blended onto the donor skin. By manual extrinsic coloring, applying lashes and eyebrows the mask was completed producing a natural appearing face and thereby preserving the dignity of the donor. This respectful approach allowed the family to greet the deceased in a serene atmosphere.

The surgical procedure

Both operations started at the same time. A tracheostomy was performed in the donor at the beginning of the procedure. Skin incisions in both donor and recipient were performed preauricular, through the lateral and medial canthi, nasion and supralaryngeal crease.

One surgical team performed the procurement, involving dissection of soft tissues and underlying bones of the mid and lower thirds of the face as calculated by the preparatory measurements. Tissue perfusion was based on the main vascular (facial artery and vein) pedicles, isolated at the inferior margin of the mandible. The entire extracranial facial nerve and sensory (buccal, infraorbital and mental) nerves were isolated and preserved for reattachment in the recipient. Bilateral superficial parotidectomies were performed. The prefabricated models and jigs were used as intra-operative guides to exactly harvest the missing part of the maxilla and mandible. A standard, allogenous radial forearm flap was harvested to be used as sentinel flap in the recipient.

The second surgical team prepared the recipient. Bilaterally, all branches of the facial nerve (except the frontal intact branch) distal to the bifurcations of the main stem were identified after performing a superficial parotidectomy, followed by the isolation of the facial arteries and veins. The buccal nerves were retrieved and marked; both mental and infraorbital nerves were destructed due to the initial trauma and could not be retrieved. The free ALT-flap from the previous reconstruction and all old hardware were removed. Osteotomies were performed at the borders of the remaining bony structures, using the jigs and the skull models. Despite nearly intact soft tissues in the right periorbital and cheek area, the decision was made to transplant the entire mid face from ear to ear as an aesthetic unit including both lower eyelids (Fig. 4.9).

At the end of the procurement, both vascular pedicles were clamped and the allograft was transferred to the recipient room on a custom-made support structure (Fig. 4.10). The face was flushed during 30 minutes with standard Histidine-Tryptophan-Ketoglutarate solution.

During the entire facial allograft recovery, there was minimal blood loss and the donor was hemodynamic stable. Thus he was suitable for solid organ recovery as

consented by the family and the transplant surgery team continued with organ procurement.
Following primary inset of the graft, the left facial artery was anastomosed end-to-end, followed by an end-to-side anastomosis of the external jugular vein. Total ischemia time of the allograft was 2 hours and 27 minutes. The entire graft was revascularized with return of the cutaneous capillary refill and full revascularization of mucosal structures. Osteosynthesis was then performed, showing clear evidence of successful bony revascularization as active bleeding from the drill holes and periosteum of the donor bone was noticed. Sequentially, the contralateral vessels were anastomosed. All individual branches of the facial nerve were coapted bilaterally, except for the frontal branch. The sensory buccal nerves were coapted bilaterally end-to-end; we performed shared nerve grafting of the right infra-orbital nerve and mental nerves to the greater auricular nerves by interposition of the donor's radial nerve as primary suturing was impossible (16). Unfortunately the left infra-orbital nerve could not be retrieved and was not repaired. The soft tissues were sutured in layers, the oral mucosa was approximated and the hard palate sutured to the soft palate. Since the lower eyelids were transplanted as well, a lateral canthopexy with additional soft tissue fixation of the cheeks to the lateral orbital wall was performed using a Mitek Anchor System (Mitek Products Inc., Westwood, Mass) to avoid ectropion and sagging of the cheek soft tissues. Finally the skin was closed using resorbable sutures and skin adhesives. The donor radial forearm flap was anastomosed to the left femoral vessels of the recipient at the site of the previously harvested ALT flap as sentinel flap easily accessible to take skin biopsies for histological evaluation. The patient required a total transfusion of 6 units packed cells and 4 units of fresh frozen plasma; the entire surgical procedure lasted for 20 hours.

Medication/Immunosuppression

The immunosuppression induction protocol consisted of intravenous (IV) anti-thymocyte globuline (ATG Fresenius 4 mg/kg/d for 7 days), tacrolimus, mycophenolate mofetil (Cellcept) and methylprednisolone 500 mg IV at incision. The maintenance immunosuppressive regimen included tacrolimus at targeted trough concentration of 10-15 ng/ml in the first months with mycophenolate 1 g bi-daily (BID) and tapered dosing of methylprednisolone to 8 mg at the end of month 3. Prophylactic treatment of *Pneucocystis jiroveci*, *cytomegalovirus* (CMV) and fungal infections was provided by co-trimoxazole 400/80 mg, valganciclovir 900 mg and itraconazol 100 mg daily PO (Fig. 4.11). For an impaired glucose tolerance testing at month 1, metformin 500 mg BID was started. Vitamin D cholecalciferol 880U with CaCO3 1 g daily was prescribed preventively for osteoporosis. The patient was daily treated with citalopram 40 mg and trazodone 100 mg until 8 months post transplant.

Results

The immediate postoperative course was uneventful and the patient was able to produce simple one-syllable words and swallow liquids six days after the transplantation. CT-scans showed nearly optimal fit of the bony elements as in a successful Le Fort III fracture realignment (Fig 4.12 and 4.13).

Logopaedic rehabilitation therapy started one week postoperatively, focused mainly on breathing, swallowing, oral motor functions and an increase of overall speech intelligibility in phonemes, syllables, words and short sentences (17, 18). Also tactile recognition of the facial structures, facial massage and mime therapy were initiated together with continuation of low-vision training. Oronasopharyngeal endoscopy on day 26 showed no signs of infection, ischemia or necrosis in the mucosa of the allograft and an adequate velopharyngeal lifting with lateral pharyngeal wall constriction during the production of the oral sound /a/ was observed as preoperatively.

Unfortunately we were not able to perfectly align the hard palate of the donor with the soft palate of the recipient due to size discrepancy. A small fistula responsible for moderate hypernasality was treated with a custom made obturator prosthesis. Oral inspection showed a Class 2 malocclusion due to overjet of the transplanted maxilla without functional problems. The patient was discharged from the hospital in good clinical condition 4 weeks after transplantation. Oral intake was normal 2 months postoperatively; the tracheostomy was eliminated 1 year after the transplantation and maximal mouth opening was 4 cm interincisal. Two years after the transplant, correction of the tracheostomy scar is planned in combination with the placement of

Brånemark implants in the left eye socket for epithetic reconstruction; eye prosthesis will be provided for the right side.

Intensive psychological and psychiatric support was provided to the patient and his partner. During 15 months post surgery period, 35 psychiatric and 26 psychological sessions took place. To date, the patient is psychologically doing well. He has no symptoms of depression, post-traumatic stress disorder or any anxiety disorder. Further, the patient reports good dyadic adjustment and healthy family functioning (19). Despite his blindness, he has successfully re-integrated in his community participating in several social and family activities and regained a good level of autonomy.

Postoperative complications

No clinical or histological signs of graft rejection were encountered during the first 15 weeks. At the end of the third month, the patient developed swelling and pain at the left jaw during eating and mime therapy exercises. CT-scan revealed an abscess on an osteosynthesis screw of the proximal mandibular osteosynthesis plate. Cultures grew *Aspergillus fumigatus* despite antifungal therapy. After surgical drainage of the abscess and removal of the screw therapy was switched to voriconazole 200 mg BID. Radiologic search for metastatic aspergillus spread in sinus and lung was negative. After 8 days of voriconazole treatment, while tacrolimus dosing had been reduced to remain within the intended 10 ng /ml range, the patient developed a hyponatriemia of 124 mmol/L due to the syndrome of inappropriate secretrion of ADH (SIADH) for which antifungal treatment had to be switched to caspofungin 50 mg IV daily maintenance.

Thirteen days after draining of the abscess, the patient developed severe redness, swelling, epidermiolysis and mucosal blistering, corresponding with grade IV rejection of the graft, histologically proven by biopsies taken from the oral mucosa. The sentinel flap on the left leg clinically showed little changes and histology of skin biopsies revealed only minor rejection. Rejection was successfully treated with methylprednisolone IV at 500 mg and hyperimmune CMV immunoglobulins IV 2 g/kg for 4 days. He also developed sinusitis due to

Pseudomonas aeruginosa successfully treated with oral ciprofloxacine 500mg BID.

Despite 40 days of IV antifungal treatment, small pulmonary nodules were discovered on CT scan suspect for aspergilloma. Caspofungin was switched to oral posaconazole 400 mg BID. He redeveloped SIADH; antifungal drugs were switched again to voriconazole 200 mg BID given orally for 52 days with decreasing pulmonary lesions on CT scan.

At month 6 an asymptomatic CMV viremia with an UL-97 gene mutation resistant to valganciclovir developed, requiring hyperimmune CMV immunoglobulins IV and further reduction of immunosuppression; Polymerase Chain Reaction (PCR) CMV viremia subsided.

At month 7 the patient developed painful osteoporotic thoracic vertebral fractures; analgesia and diphosphonate zoledronic acid were started in combination with wearing an orthopaedic corset.

At month 8 he experienced stupor for two days related to a hyponatremia (116 mmol/L) due to a SIADH caused by the citalopram treatment in combination with fentanyl patches treatment for the fractures pain.

At month 11 the pulmonary aspergilloma relapsed with clinical symptoms of fever and radiologic progression. The patient had to be hospitalized for IV treatment with Abelcet amphotericin B lipid complex 5 mg/kg during 3 weeks. Unfortunately nephrotoxicity developed, antifungal therapy was switched to Ambisome liposomal amphotericin B 3 mg/kg during 2 weeks resulting in clinical and radiological remission; a superimposed *Pseudomonas aeruginosa* pneumonia was successfully treated by IV tazobactam 4 g X 4 daily. Since then the clinical situation remains remarkably stable and the patient is doing well. Minimal rest lesions on pulmonary CT scan and negative blood galactomannan are suggestive of cured *Aspergillus* infection.

Functional recovery of the facial allograft

First fasciculations in the orbicularis oris muscle were seen at week 13. The first active and controlled smile movement without synkinesis was observed at 4 months. Six months postoperatively, the patient was able to lift the oral commissure independently left and right, the nasolabial folds were again present and non-verbal communication and facial expressions were returning. Mouth closure turned into nearly normal after disappearance of the initial swelling and with improved tonicity of the soft tissues.

At 24 months follow-up the patient reported recovery of sensation in the transplanted face with better sensation right than on the left side; independent voluntary movements of both sides of the face were possible without mass movements or synkinesis (see Fig. 4.14 and 4.15 which show the 2-year postoperative appearance of the face).

Discussion

In this patient, 3D models and digital planning have been used for the first time to perform a facial VCA. In previous osteomyocutaneous face transplantations, no specific techniques have been described to provide a solution for the problem of the measurements of the graft and the fitting in the recipient defect; issues essential for obtaining good aesthetic and functional outcomes. Based on our experience with 3D-CT modeling in facial surgery and anaplastology, we have implemented this concept to VCA of the face as well. It has already been used in the planning of craniofacial, orthopaedic and cardiac surgical procedures and has shown its efficiency producing excellent functional and precise results (20 - 23). We believe that digital planning and 3D models in face transplantation not only allow the surgeons to harvest the exact amount of bone needed in the donor but also to precisely prepare the recipient site. They can be valuable tools in cases where an extensive osteomyocutaneous graft has to be transplanted thus simplifying and shortening a complex surgical procedure. We experienced a Class 2 malocclusion; maybe this could have been avoided by applying digital planning to the actual donor and superimposing the facial skeleton onto that of the recipient as shown by Rodriguez et al. (24). However this is more time consuming, superimposing risks concerning the hemodynamic stability of the donor and interfering with the timing of the subsequent organ transplant surgeons. Also no preoperative printed models and jigs can be generated. The 3D imaging has helped us a lot to save operating time, to determine the amount of bone needed in the upper and lower jaw to obtain a result as good as possible taking all factors into consideration. The absence of a perfect occlusion is due to the discrepancy between the donor and recipient bony structures. It could only have been resolved if mandibular osteotomies would have been performed during this transplantation setting. Not only was the planning of such a potential osteotomy not possible due to the acute situation, but it would definitively have jeopardized the vascularity of the involved bony fragments as well. We have therefore tried to obtain the best dental relationship as possible considering these factors with the option to perform corrective osteotomies at a later stage.

As the sensory nerves of the lower part of the face in our patient were destructed due to the initial injury, we performed shared nerve grafting for sensory restoration of the allograft (16). We already had anticipated on the fact that it would be impossible or very difficult to retrieve these nerves deep in the face and planned the nerve sharing technique for sensory repair in order not to lose operative time during the transplantation performing difficult microsurgical nerve repair. Nerve sharing is a technique for restoring sensory or motor innervation to a denervated area by supplying axons from a distant dermatome. A subpopulation of axons is diverted so that the dermatome of the donor nerve is only partially denervated. We used the anterior branch of the greater auricular nerve to reinnervate the skin area of the right infraorbital nerve and both mental nerves with the interposition of a radial nerve graft. The effect of this sensory reinnervation is that the patient could possibly locate stimuli to the face in or near his right ear. Interestingly, the patient experienced stimuli to the right side of the face at 8 months during the sensory assessment but he could not localize these stimuli correctly. Later on, he experienced no issues in correct localization of the stimuli, additionally, hyperesthesia was not noticed; it seems that the central nervous system is plastic enough to adapt following nerve sharing.

So far, 34 face transplantations have been performed worldwide including our case (14, this thesis chapter 1). Five deaths occurred, mainly related to the side effects of the immunosuppressive treatment. The indications were traumatic injury in 27 cases, neurofibromatosis in 4 cases, facial deformity after tumor resection in 2 cases. VCA has become a feasible and reproducible surgical procedure as many technical, logistic, social and immunologic issues have been improved or resolved during the last decade. VCA should be taken into consideration as an early option in extreme cases not amenable to modern-day reconstructive surgery to spare the patient years of continued disfigurement both in the face and donor areas, facial malfunctioning and the cumulative financial and psychological burden of multiple reconstructions (25 - 31). The extensiveness and the complexity of the defect to the central most mobile area of the face of our patient and the expected poor postoperative clinical and functional outcome after reconstruction made it very likely that further conventional reconstructive surgery would be a long lasting process requiring multiple procedures with inferior results (32, 33). Therefore allotransplantation of the face was considered in an early phase as the best option on the long term to re-establish vital functions, aesthetics and overall quality of life in a one-staged procedure.

We experienced one episode of a proven grade IV rejection. At the same time, the sentinel flap on the left leg showed minimal clinical and histological changes during this rejection; this in contrast to the clinical aspect and biopsies of the facial allograft. This contradictory phenomenon has been observed by some others (14, 34) but not all (7, 27). Possible reasons may include the differences in tissue composition of the face (compound) and sentinel (skin) flap, the latter being less antigenic. The cellular and molecular basis for skin rejection in VCA, although partially delineated, remains largely unknown and there are only few reports on the pathology of face transplant (35, 36). The diagnosis of rejection in VCA is a major challenge and the final decision upon diagnosis and treatment should be made based on both clinical signs and histological findings of skin/mucosa biopsies.

The main drawbacks of facial transplantation are not associated with the allograft itself but the need for life long immunosuppressive therapy with associated long-term side effects (opportunistic infections, secondary malignancies and cardiovascular morbidity) and potential mortality. During the 12 months post surgery period, our patient also suffered from many and severe medical complications mainly caused by the pharmacological treatment. As a result he was frequently hospitalized, underwent different medical treatments and experienced a decreased physical quality of life. A continuous multidisciplinary treatment of these patients is an absolute need; being under immunosuppression, they turn chronically ill and the impact of associated complications not only affects them but also poses a severe burden to the family. Despite all, our multidisciplinary team agreed that the approach would not be have been different. Also the patient mentioned he would have gone through with the procedure.

Until now, four blind patients including our case received facial transplantation and there has been controversy whether to perform this procedure in blind patients or not, based on functional, social, rehabilitative and ethical concerns (37). Before transplantation our patient was already well adapted to his handicap due to early rehabilitation. We experienced no issues with compliance to rehabilitation, surveillance of the graft, and identity transfer (17 - 19). He demonstrated good recovery of motor and sensory function and good social reintegration with improved quality of life similar to non-blind face transplant patients. In our opinion blindness is not a contraindication in well-selected and motivated face transplant candidates. Blind patients might even have more psychological benefits of the knowledge of having a normal facial appearance and not being stared at in a crowd.

In the first described cases of facial transplantation the aesthetic subunits were considered of less importance. In our patient, the defect was mainly located on the left side of the face but the decision was taken to transplant the soft tissues of the entire lower two thirds of the face as aesthetic units to avoid a patchy, mutilated appearance. If failure would have occurred due to uncontrollable rejection or infection, traditional free flap reconstruction with ALT flap, DIEP flap, fibula flap and latissimus dorsi flap was still possible in our patient, as these flaps were not used in previous reconstructions. This in contrast to other reported cases, where many patients already had undergone numerous reconstructions, leaving them depleted from spare flaps if transplantation would fail. In our patient, the transplantation of entire facial subunits simplified facial allograft recovery and favored a more aesthetically pleasing result; this strategy was based on the advice and experience of other authors (31, 38 - 42). The graft integrated into the native skin of the forehead without major differences in color, texture or contour. The facial morphology and appearance improved with time without requiring revision surgery.

Conclusion

In our experience, 3D CT-modeling, preparatory cadaver dissections and a meticulous planning with a multidisciplinary team have proven to be valuable tools for a fluent intra-operative course, adequate bony alignment and good functional and aesthetic outcome in the first Belgian face transplant. These findings are in accordance with other reports and hopefully will contribute to further support and optimize facial transplantation and outcomes.

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Disclosure

None of the authors has any financial conflicts of interest in any of the products, devices or drugs mentioned in this article.

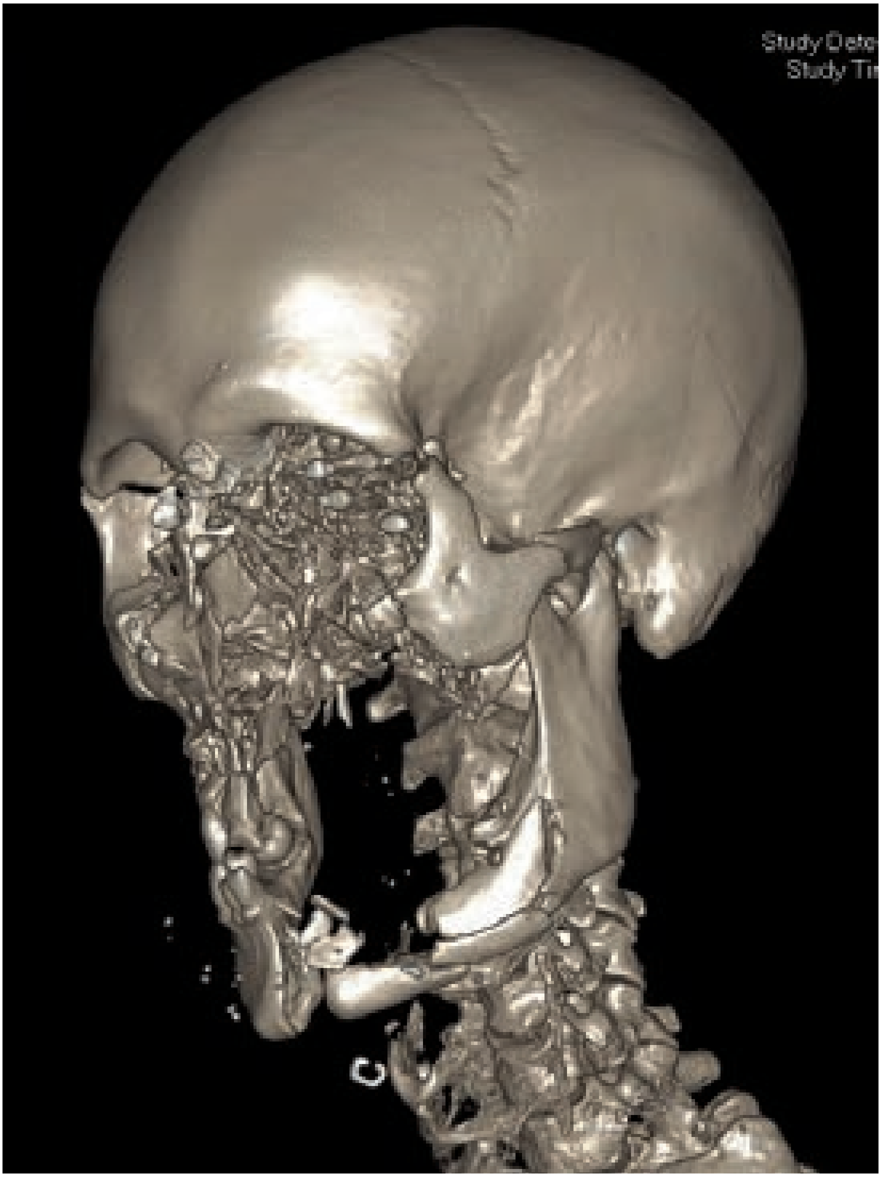

Figure 4.1:

Left three-quarter view of the preoperative 3D CT-scan of the patient, showing missing facial bony structures: bilateral medial orbital wall and floor, nasal bones, bilateral maxillary complex, hard palate including dentition, horizontal part of the left mandible.

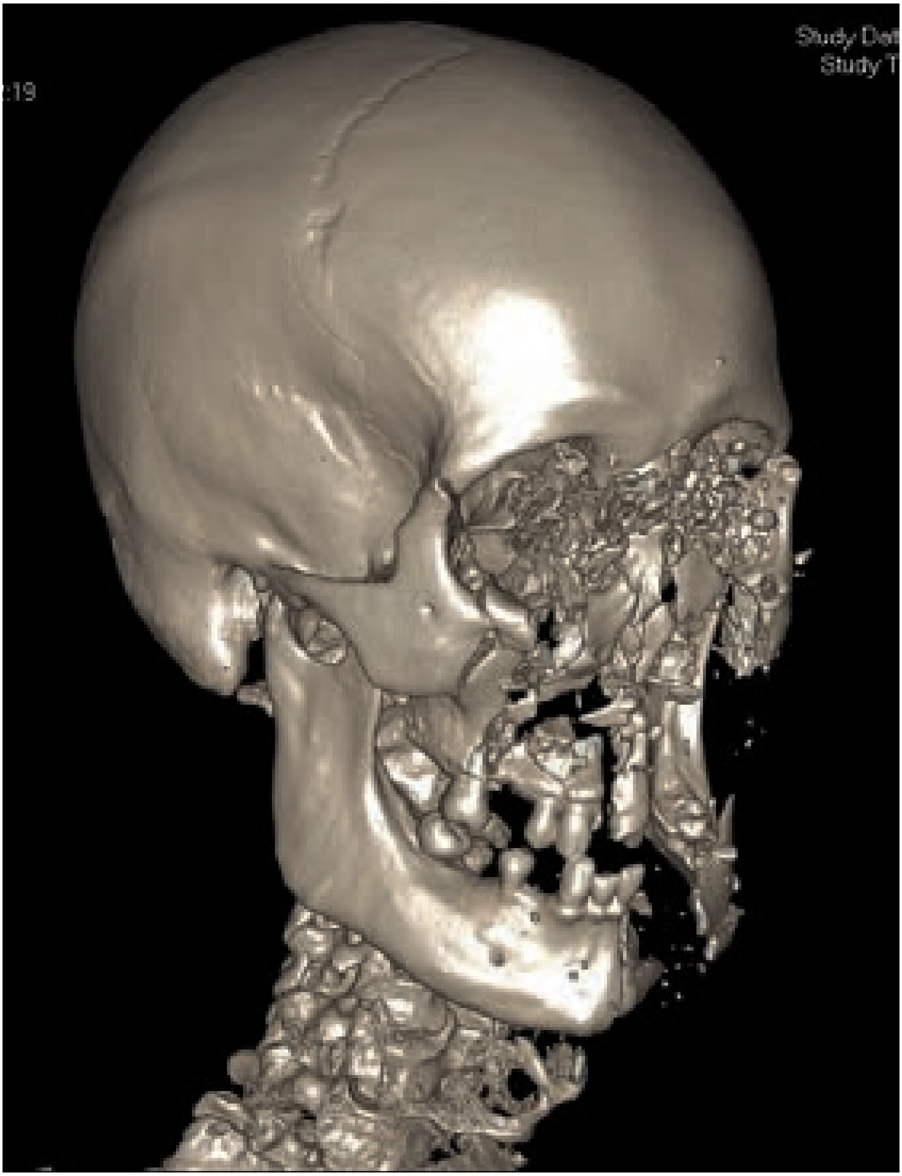

Figure 4.2:

Right three-quarter view of the preoperative 3D CT-scan of the patient.

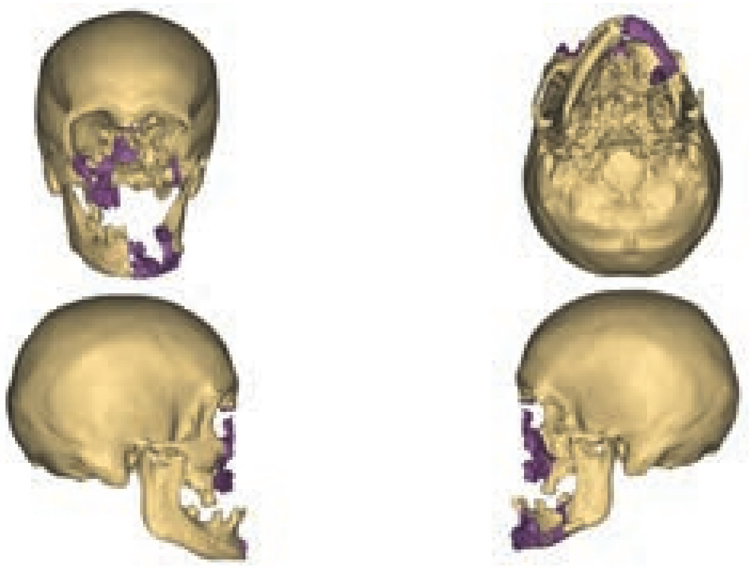

Figure 4.3:

3D CT-scan of the preoperative situation in recipient. Purple indicates the bony parts of the maxilla and mandible to be resected before placing the allograft.

Figure 4.4:

Frontal view of the patient before transplantation after temporary reconstruction with a plicated free ALT flap.

Figure 4.5:
Lateral view of the patient, note loss of midface projection, incapacity to close the mouth, submandibular fistula needing continuous wound dressings.

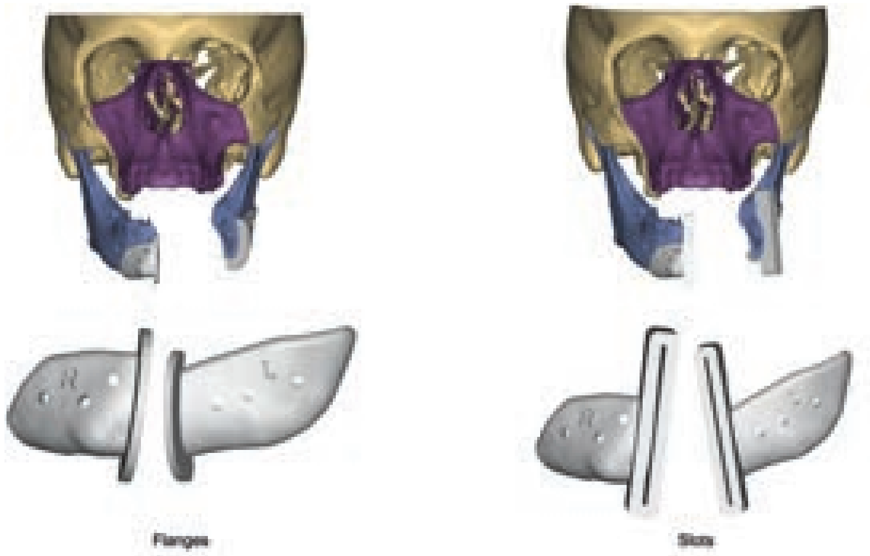

Figure 4.6:
3D models of the recipient with maxilla graft in place (top) and mandible resection guides (bottom) used in recipient.

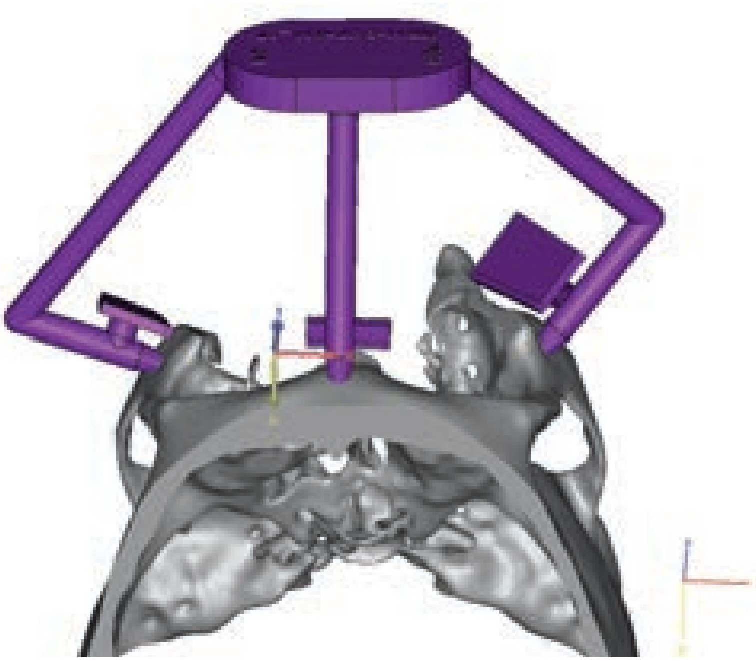

Figure 4.7:
Cranial view of the 3D model of the maxilla resection guide, used to determine the correct plane and position of the osteotomies in recipient.

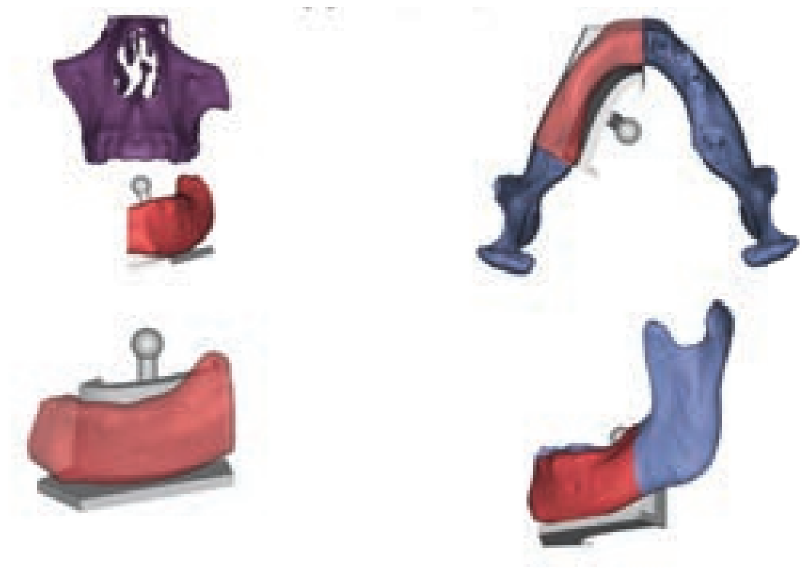

Figure 4.8:

3D models of the maxilla and mandible graft (top left) and 3D models of the mandible harvesting guides used in donor (top right: caudal view; bottom: lateral views).

Figure 4.9:

Resected lower 2/3rds of the face in the recipient, including the ALT-flap from the previous reconstruction and nearly intact soft tissues on the right side of the face.

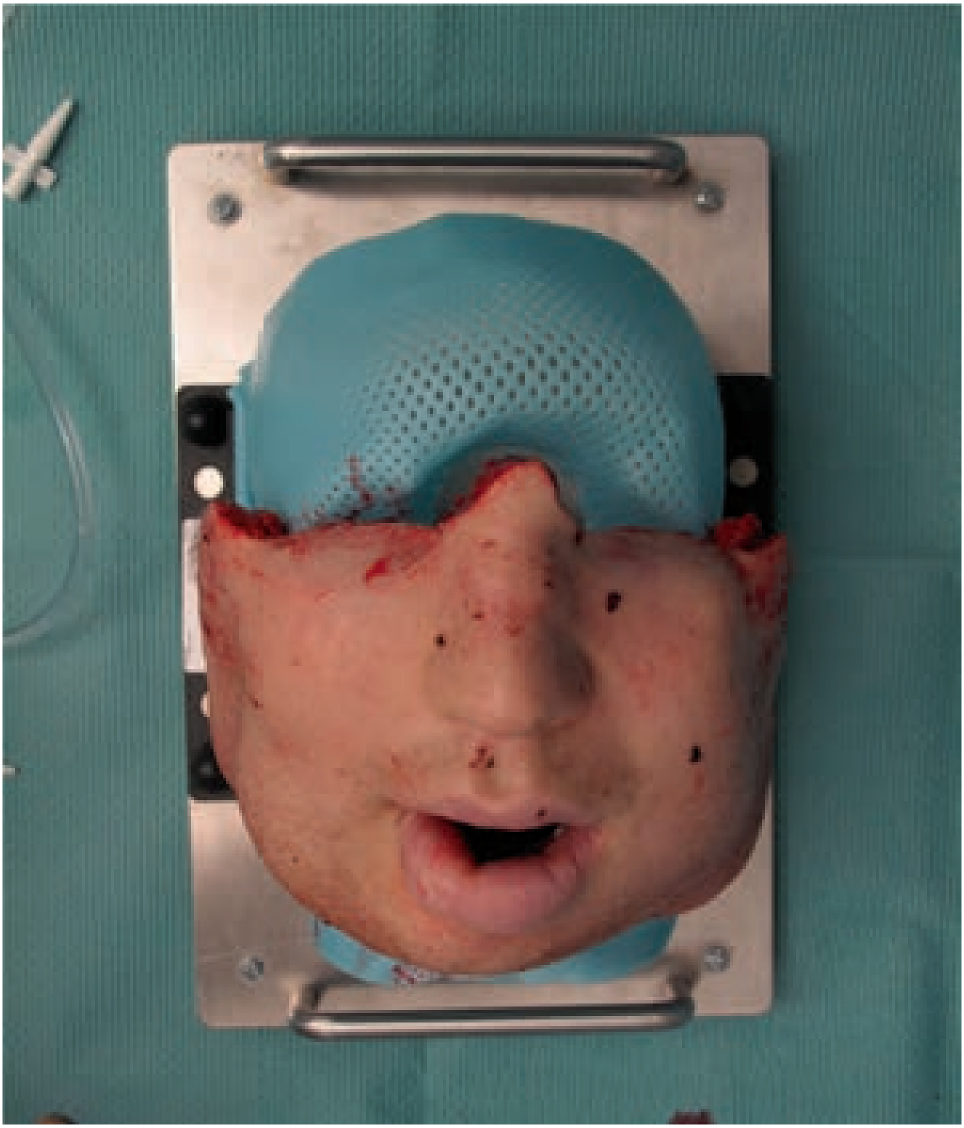

Figure 4.10

Custom-made support structure to transport the facial allograft and to facilitate preparations/surgical handling necessary before the actual transplantation.

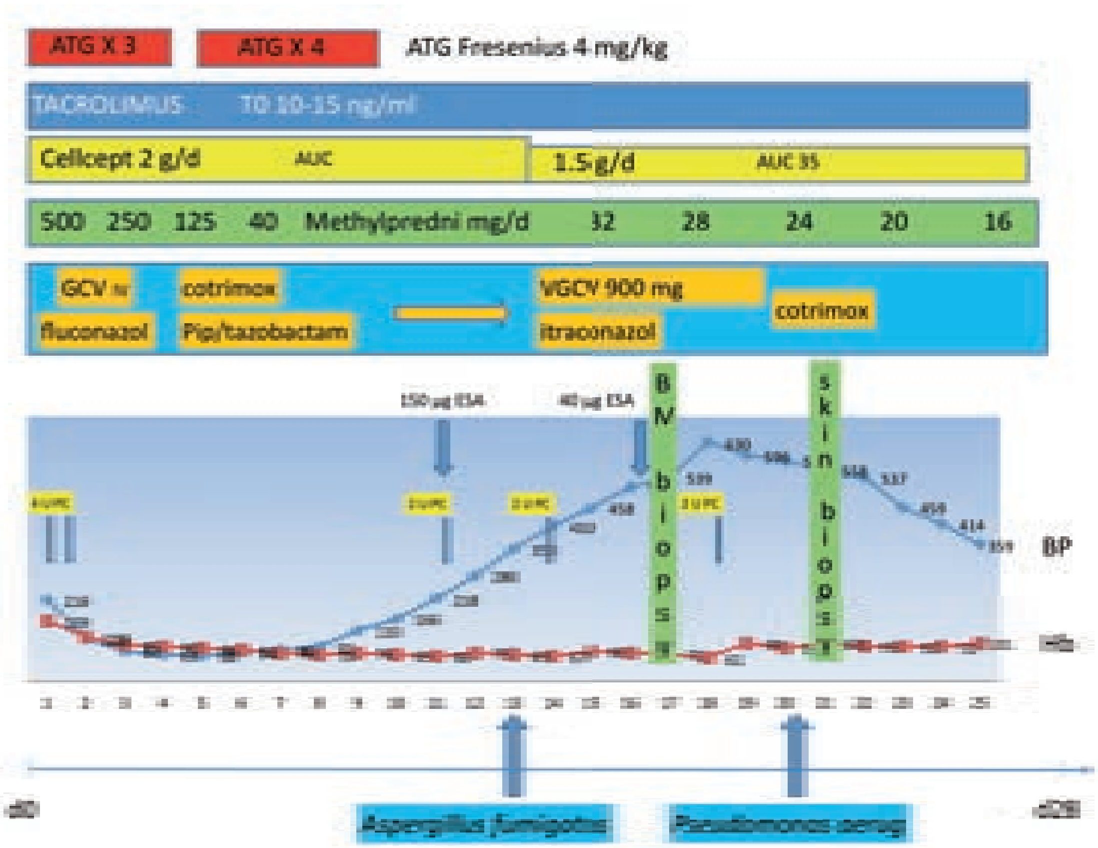

Fig 4.11:

Schematic representation of medication/immunosuppression given in the first month after the transplantation.

ATG = anti-thymocyte globuline

TO = targeted trough, AUC = area under the curve

GCV = ganciclovir, VGCA = valganciclovir

PC = packed cells, ESA = erythropoiesis-stimulating agent

BM = bone marrow, BP = blood platelets, Hb = Hemoglobin

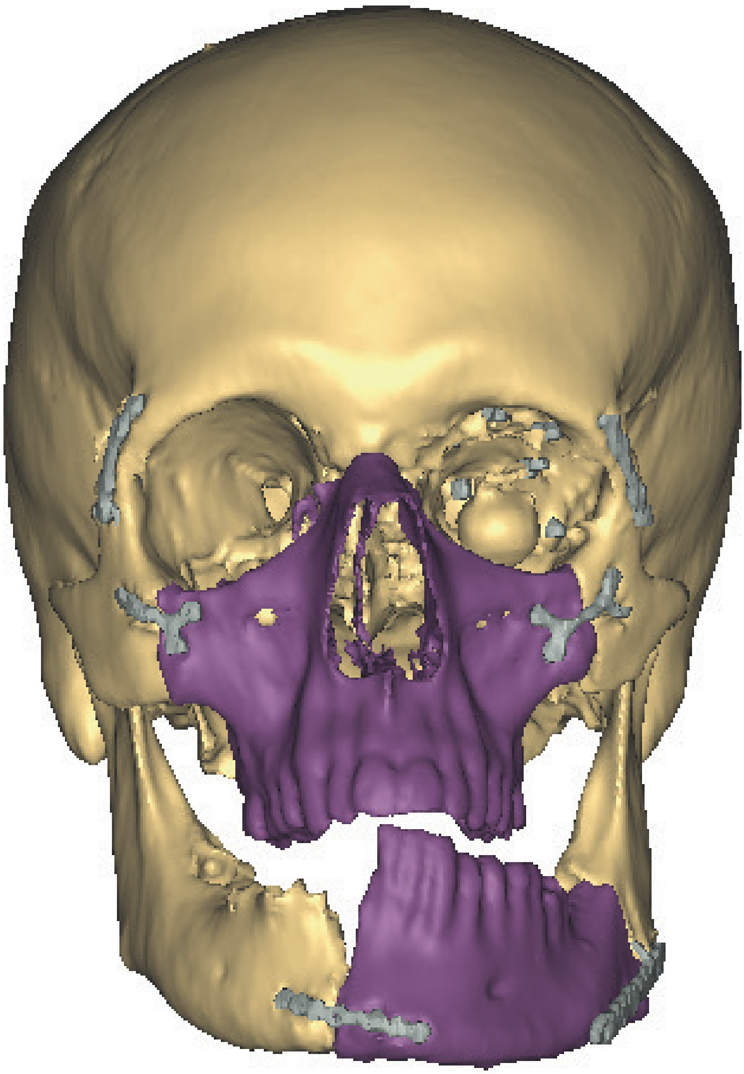

Figure 4.12:

Postoperative 3D CT-scan with allograft (purple) in place, showing good bony alignment.

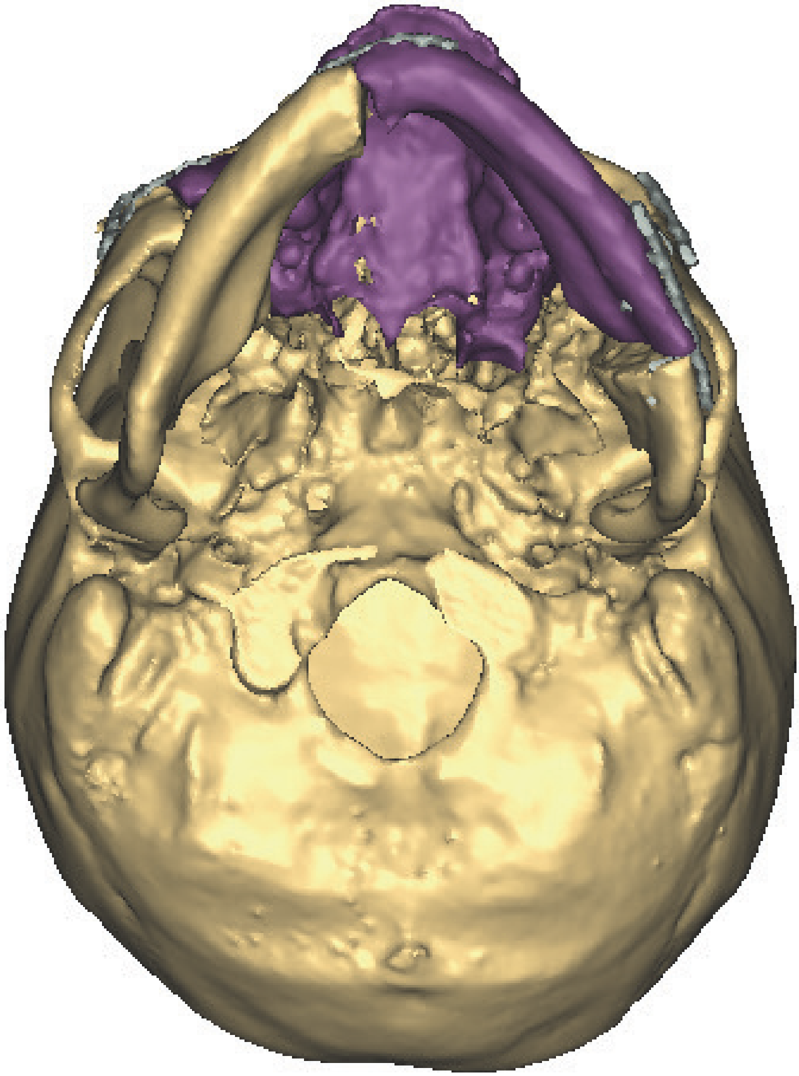

Figure 4.13:

Postoperative 3D CT-scan, basal view with allograft (purple) in place.

Figure 4.14:

23-month postoperative frontal view of the patient.

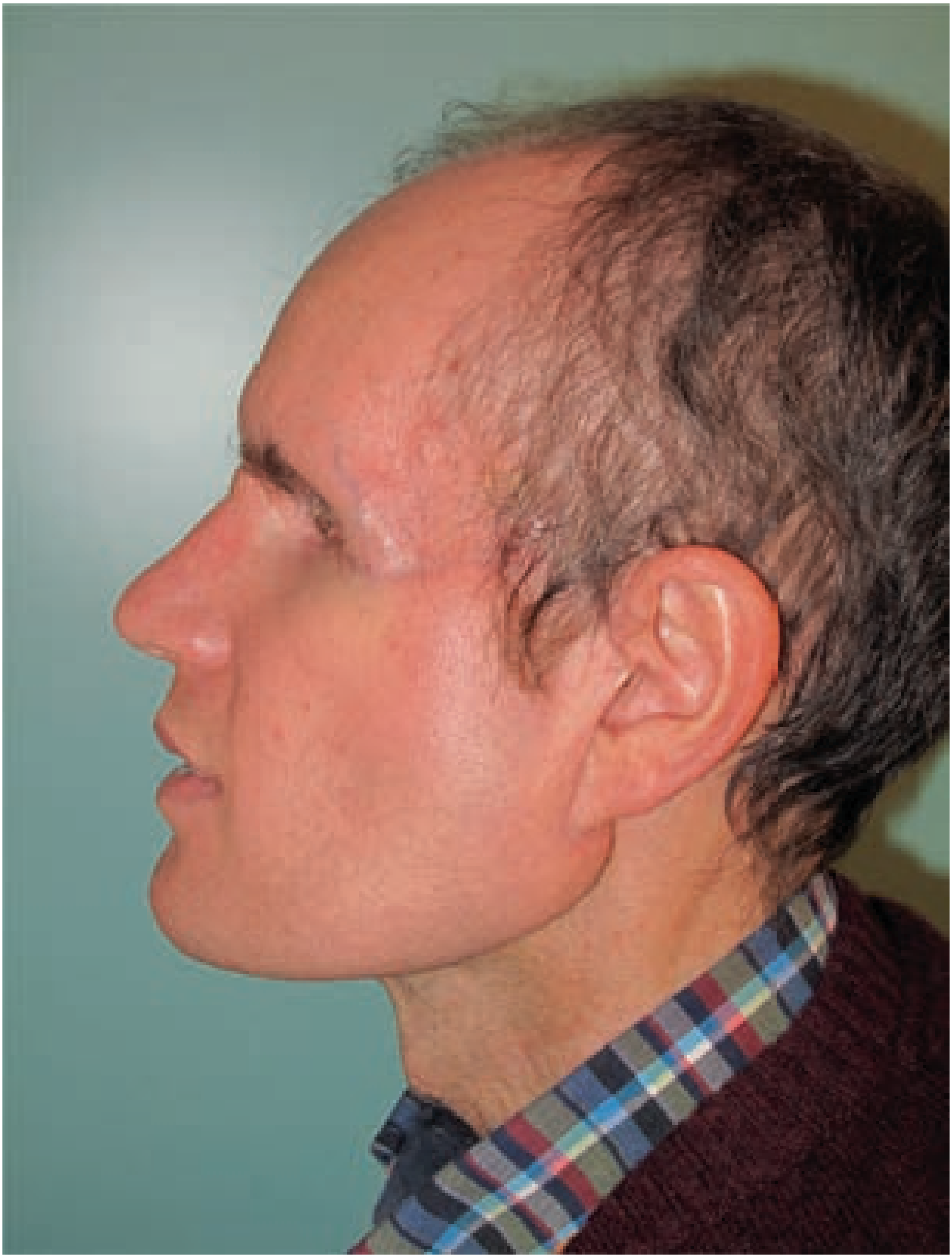

Figure 4.15:

Lateral view of the patient, note good midface projection and skin color match.

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CHAPTER 5

Speech characteristics one year after first Belgian facial transplantation

Based on:

Kristiane M. Van Lierde*, Nathalie Roche*, Miet De Letter, Paul Corthals, Filip Stillaert, Hubert Vermeersch, Phillip Blondeel. Speech characteristics one year after first Belgian facial transplantation. *Laryngoscope. 2014 Sep;124(9):2021-7.*

*These authors contributed equally

Abstract

Objective: Facial transplantation has progressed over the past 8 years. We did the first Belgian facial transplantation by vascularized composite tissue transplantation and report the 1-year follow-up regarding speech and oromyofunctional behavior.

Study design: Outcome study

Methods: The recipient, a 54-year-old man had his face severely injured due to a ballistic injury. In December 2011 in a 20-hour surgical procedure, a digitally planned facial composite tissue allotransplantation was performed consisting of a large amount of bone together with the soft tissue of the entire lower 2/3rd of the face. Speech intelligibility, voice, resonance, articulation and oromyofunctional behavior were measured 12 months after the transplantation using objective and subjective assessment techniques.

Results: No intra-operative surgical complications occurred and the immediate postoperative course was uneventful. Survival of the graft was complete, the bony structures - both maxillae and part of the left mandible - and mucosal lining of the nasal cavities and hard palate could all be vascularized by connecting only the facial vessels. Twelve months after transplantation the speech intelligibility is normal in words, but slightly impaired in sentences due to moderate hypernasality. Two articulation disorders and lip incompetence are present. Facial emotional readability was present but decreased.

Conclusion: Speech outcome, as one of several determinants of feasibility, can be a positive argument when considering the option of facial allotransplantation.

Key Words

Speech; Facial transplantation; Vascularized composite tissue allotransplantation; Functional recovery; Face allotransplantation

Introduction

Since 2005 34 facial transplants were performed (1 - 15). In most of these cases the surgical and immunological outcomes are very well described. Most studies that have examined the functional outcome focused on the ability to swallow, to eat and to move the lips (Table 5.1).

The most detailed description of functional outcome is available for the first face transplantation (3 - 5) performed by Devauchelle et al. (3). Five years after transplantation this patient could smile, chew, swallow, and blow normally whereas pouting and kissing remained still difficult. Moreover this patient could talk easily and intelligible. In the reports of Lantieri et al. (7, 9) and Siemionow et al. (8) the patients were reported to be able to speak (7) and to produce intelligible speech (8, 9).

Comparison between the functional outcomes of the reported face transplant cases is very difficult, – taking into account the uniqueness of each defect, - and because results from objective assessment techniques or consensus perceptual evaluations are not available in these studies. Moreover very few authors reported detailed analyses of the outcome regarding overall intelligibility, speech characteristics and the interactive processes (voice, resonance, articulation) of speech. According to Siemionow and Gordon (16) all facial transplant teams have a responsibility to publish their outcomes in a transparent manner in order to contribute to the international field.

The purpose of this study is to document overall speech intelligibility (SI), voice, resonance and articulation characteristics one year after a complex facial reconstruction by vascularized composite tissue allotransplantation. Detailed information on speech characteristics after facial transplantation leads to better guidance of patients after a face transplantation. A detailed protocol for speech assessment after facial transplantation is described in order to better define speech rehabilitation for these unique patients in the future.

Materials and methods

This research was approved by the Ethics Committee (2012/809) of the Ghent University Hospital.

Subject

A 54-year-old man was admitted to the emergency department in December 2010 due to a ballistic injury to the face. He presented with a major soft tissue defect of the lower two thirds of the face and an extensive loss of facial bony structures, both maxillae and left part of the mandible. Vision was lost, as both eyes were involved. A thorough description of the initial reconstructive surgery as well as the digitally planned facial composite tissue allotransplantation (CTA) of the entire lower 2/3rd of the face that was performed in the patient is provided in chapter 4 of this thesis.

No intra-operative surgical complications occurred and the immediate postoperative course was uneventful. The patient was able to swallow liquids and to produce vowel speech six days after the transplantation. Speech rehabilitation started one week postoperatively, 5 times a week (first three months) and focused on breathing, swallowing, oral motor functions, overall speech intelligibility, voice, resonance and articulation of phonemes, syllables, words and short sentences. After three months the frequency of therapy reduced to 3 times a week. The patient is very dedicated to the speech therapy and the partner is functioning as a co-therapist. Also tactile recognition of the facial structures and facial massage were initiated together with low-vision training. Oropharyngeal endoscopy on day 26 postoperative showed no signs of infection, ischemia or necrosis in the oronasal cavity. Regarding the velopharyngeal mechanism an adequate lifting of the soft palate with lateral pharyngeal wall constriction during the production of the vowel /a/ was observed (100% consensus evaluation, HV, KVL). A fistula located between the hard and the soft palate was present, responsible for the presence of moderate hypernasality (i.e. excess resonance of vowels and voiced consonants within the nasal cavities). An obturator prosthesis was made to restore the anatomy between the oral and nasal cavity. Sensory/motor recovery started 4 months postoperatively. Clinical signs of one acute rejection were diagnosed 3 months postoperatively with total recovery. One year after transplantation the patient was very satisfied with the aesthetic outcome and social re-integration in the community is successful. Pure-tone testing revealed normal hearing sensitivity in both ears.

Methods and materials

Objective and subjective assessment techniques and questionnaires were used to determine the speech characteristics (overall intelligibility, voice, resonance and articulation characteristics) and oromyofunctional behavior 12 months after facial transplantation. The speech assessments were performed independently by two speech pathologists (KVL, MDL), who were not involved in the daily speech training sessions. During the assessments the patient was not wearing the palatal obturator.

Speech intelligibility

Speech samples, collected by means of a picture-repeating test (see articulation) were used to judge overall speech intelligibility of words, sentences and during spontaneous speech using an ordinal scale with four levels (0= normal speech intelligibility, 1= slightly impaired, 2= moderately impaired and 3= severely impaired speech intelligibility). All analyses were based on a consensus narrow phonetic transcription made by two experienced speech pathologists (KVL, MDL), using the symbols and diacritics of the International Phonetic Alphabet. The speech language pathologists first simultaneously but independently transcribed the samples before comparing transcriptions aiming at a consensus.

The Dutch speech intelligibility test (17) was applied requiring the patient to repeat words and sentences. These speech samples were videotaped and subsequently transcribed by the same two speech language pathologists in order to calculate the percentage of sounds produced correctly.

The Spraak Handicap Index (SHI), the Dutch version of the Parole Handicap Index (18) is a self-assessment questionnaire reflecting the functional (5 questions), physical (5) and psychological (5) impact of a speech disorder on the quality of life. The subject has to respond according to the appropriateness of each item (0= never, 1= almost never, 2=sometimes, 3= almost always, 4= always). The final result varies between 0 and 60, with the latter representing a maximum perceived impact of the speech disorder on the overall quality of life.

Voice

Subjective assessment*:* Voice assessment included a flexible *videolaryngostroboscopy* and a *consensus perceptual rating of the voice* during connected speech. Voice rating was performed by two experienced speech language pathologists (KVL, MDL) using the *GRBAS scale* (19). The GRBAS assessment consists of five well-defined parameters: G (overall grade of vocal pathology), R (roughness), B (breathiness), A (asthenicity), and S (strain). A sixth parameter, I for instability of the voice was added to the original scale. A four-point grading scale (0= normal, 1=slight, 2=moderate, and 3=severe) is used to indicate the grade of every parameter. In addition to GRBASI assessments, vocal pitch and intensity were judged as “normal”, “increased” or “decreased”. Voice samples of connected speech during reading were audio-recorded for further analysis. The speech pathologists first independently rated each voice sample. In case of disagreement, the voice samples were replayed and discussed aiming at a consensus score.

The Voice Handicap Index (VHI) was used to measure the subject’s perceptions of his psychosocial impact of the vocal problem. The VHI is a useful instrument for quantifying the bio-psychological impact of voice disorders (20). The VHI is a self-administered questionnaire that consists of 30 questions or statements. The subject has to respond according to the appropriateness of each item (0= never, 1= almost never, 2=sometimes, 3= almost always, 4= always). The VHI score varies between 0 and 120, with the latter representing the maximum perceived disability due to vocal difficulties.

Objective assessment*:*

Aerodynamic measurement: The Maximum Phonation Time (MPT) was measured on the basis of two test trails with the vowel /a/, sustained at the subject’s habitual loudness and pitch in free field and in sitting position. The duration of the sustained phonation was measured in seconds with a chronometer. The patient received verbal and visual encouragement and coaching during this vocal task. The best of both trails was retained for further analysis.

Vocal range: Frequency and intensity range were measured using with the Voice Range Profile function in the Computerised Speech Lab (CSL) (Kay Elemetrics, Lincoln Park, NJ, 1992) (21). The patient was instructed to inhale in a comfortable way and produce the vowel /a/ for at least 2 seconds, using a habitual pitch and loudness, a minimal pitch (F-low), a minimal intensity (I-low), a maximal pitch (F-high), an a maximal intensity (I-high), respectively.

Acoustic analysis: For the determination of the acoustic parameters, the Multi Dimensional Voice Program (MDVP) from the CSL (Kay Elemetrics Corp, Lincoln Park NJ) was used. The subject was asked to sustain the vowel /a/ in a comfortable way. A midvowel segment from 3 seconds registered with a sampling rate of 50 000 Hz was used for analysis. The parameters jitter (%) (perceived as hoarseness) and the fundamental frequency (F_0 in Hz) were determined.

Dysphonia Severity Index (DSI)(22)*:* The overall objective vocal quality was measured by means of the DSI, which is designed to establish an objective and quantitative correlate of perceived vocal quality. The DSI is based on the weighted combination of the following set of voice parameters: MPT (seconds), highest frequency (F-high in hertz), lowest intensity (I-low in decibel), and jitter (%). The DSI equation: (0.13 x MPT) + (0.0053 x F0-high) – (0.26 x I-low) – (1.18 x jitter) + 12.4. The DSI score ranges from +5 to -5, corresponding with normal and severely dysphonic voices respectively (i.e. the more negative the DSI value, the worse the patient's vocal quality).

<u>*Resonance*</u>

<u>Subjective assessment*:*</u> Flexible *naso-endoscopic evaluation* of the velopharyngeal valve was performed during speech and was perceptually judged by two clinicans (HV, KVL). To evaluate the degree of perceived hypernasality and/or nasal emission in words and sentences, an ordinal scale with five categories was used (1=normal resonance, 2=mild hypernasality/nasal emission, 3=moderate, 4=severe, 5=very severe). Nasal emission is defined as abnormal flow of air (audible or not) from the nares during the production of high-pressure consonants. In *the hypernasality and nasal emission test* designed by Bzoch (22) the patient is asked to repeat a series of 10 words, alternately closing and opening the nares. The scale for all words tested ranges from 0 to 10, with 0 corresponding to normal resonance and 10 with abnormal resonance. Words and sentences produced during the picture-naming test were scored by two speech pathologists (KVL, MDL). They first scored the samples independently,

and in case of disagreement, the sample was replayed and discussed until a consensus could be reached.

Objective assessment: The *Nasometer* (model 6300), a microcomputer-based system manufactured by Kay Elemetrics, was used for measurement of the nasalance values. Prior to initiating data collection, the Nasometer was calibrated following the procedure outlined in the manual. The patient was asked to sustain three vowels (/a/, /i/, /u/) and to read two nasometric passages. The “Rainbow passage”, an oronasal text with 9.7% (31/318) nasal sounds, and the “Zoo passage”, a text containing only oral sounds were read to detect the presence of hypernasality and/or nasal emission.

Articulation

Subjective assessment: Speech samples for the assessment of articulation were elicited by means of a *picture-repeating test*. This test requires the speech therapist to name black and white drawings of common objects and actions, the verbal label of which is then to be repeated (by the patient). The speech samples thus collected consisted of 135 different words, containing instances of all Dutch sounds, and of most consonant clusters in all possible syllable positions. The samples were recorded digitally for further analysis in a sound-treated room of the speech, language and hearing department at the Ghent University. The evaluation included a phonetic inventory and a phonetic analysis. The phonetic inventory reveals which consonants and vowels the patient was capable of producing correctly in his native language. This analysis was conducted without making reference to the intended target sounds. A sound was considered to be present in the inventory when at least two instances of correct productions (i.e. consistent with the standard realization of the sound) were found. In the phonetic analysis, consonant and vowel productions were compared with target productions and analyzed for error types on the segment level. All analyses were based on a consensus narrow phonetic transcription made by two experienced speech pathologists (KVL, MDL) using the symbols and diacritics of the International Phonetic Alphabet. The speech language pathologists first simultaneously but independently transcribed the samples before comparing transcriptions aiming at a consensus.

Objective assessment: To describe the quality of vowel production an *objective acoustic analysis of formant frequencies* was used (see figure 5.1). The first two formants (F1 and F2) are considered to be the most important because, based on those two formants, a listener will be able to identify a given vowel. Determination of F1 and F2 frequencies of vowels offers the possibility to describe vowels in terms of high/low and front/back placement of the tongue in the oral cavity. Also, the effect of lip protrusion is reflected in the frequencies of both formants in that rounded vowels have an overall lower formant structure. The vowels /a/, /i/ and /u/ represent the extreme articulatory positions of the tongue in English as well as in Dutch. Representing the formant frequencies of these vowels in an F1:F2 diagram yields a so-called 'vowel triangle'. This triangle is a graphic representation of the articulation space for vowel production with /a/, /i/ and /u/ as 'corner vowels'. In subjects with speech disorders, several abnormalities concerning formant frequencies and vowel space are described such as centralization of formants frequencies, the correlate of reduced articulation movements, which implies a smaller vowel triangle size. The vowels /a/, /i/ and /u/ were recorded in a sound booth in the Ghent University. Ten midvowel fragments with stable formant patterns were selected (using visual inspection of the oscillogram and the spectrogram). The 50th percentile values of F1 and F2 were measured for each vowel using the Burg algorithm in Praat software (24). The euclidian distance between the corner vowels along the axes of an F1:F2 scatter plot as well as the surface area of the vowel triangle were calculated using a Praat script. The outcome can be compared to typical formant values in the speech of adult males.

Oromyofunctional assessment

During *oromyofunctional assessment*, five functions were judged as proposed in the protocol of Lembrechts et al. (25). These functions were lip function (lip position at rest, lip closure, dispersion of the corners of the mouth, lip protrusion, lip strength, lip position during swallowing), tongue function (tongue position at rest, tongue protrusion, tongue retraction, tongue lifting against the upper lip, tongue depression against the lower lip, lateral movements of the tongue, tongue position during swallowing), blowing, sucking, swallowing and the presence of drooling. Also the *facial emotional readability* (smiling/surprised/sad/angry) was judged. A three-point rating scale was used (0=normal function, 1=decreased function, 2= function impossible). The abovementioned speech pathologists (KVL, MDL) first rated independently. In case of disagreement, the samples were replayed and discussed until a consensus was reached.

The Dutch version of the *Oral Health Impact profile* (OHIP-14) was used (26). The OHIP-14 is a self-filled questionnaire that focuses on seven dimensions of oral health impact. The domain 'functional limitation' (two questions) concerns the loss of function of parts of the body, like difficulty with chewing. The domains 'physical discomfort' (two questions) and psychological discomfort (2) deal with experiences of pain and discomfort, such as toothache and feeling miserable. The domains 'physical disability' (2), psychological disability (2) and 'social disability (2) refer to limitation in performing daily life activities, like avoiding certain foods, lack of concentration and feeling irritable with others, respectively. Finally, the domain 'handicap' (2) concerns a sense of disadvantage in functioning, like suffering financial loss because of dental problems. Answers to the 14 questions are scored on a five-point ordinal scale, ranging from 'never' (score 0), 'hardly ever' (score 1), 'occasionally' (score 2), 'fairly often' (score 3) to 'very often (score 4). Thus, higher scores imply a more impaired oral health-related quality of life. The 14 scores are summed yielding a global result (ranging from 0 to 56). Similarly, separate domain scores can be obtained. The patient was also asked to rate overall 'oral health' satisfaction with the transplanted oral cavity on a visual analogue scale with 100% reflecting complete satisfaction and 0% corresponding to completely not satisfied.

The Facial Disability Index (FDI) is a reliable and valid self-report questionnaire of physical disability (5 questions) and psychosocial factors (5 questions) related to facial neuromuscular function (27). The FDI can be used as an initial assessment tool and as a monitoring instrument, providing the clinician with the patient's view of the outcome in the intervention progress. The scores on the physical and psychosocial scale are transformed to a 100-point basis (with 100 % reflecting no facial disability).

Results

A summary of the assessments results for speech intelligibility, vocal characteristics, resonance, articulation and oromyofunctional behavior is provided in table 5.2.

Speech intelligibility

Overall speech intelligibility is judged as normal for isolated words (score 0) and slightly impaired in sentences and during spontaneous speech (score 1) (consensus evaluation 100%). The total score on the "Spraak Handicap Index" (speech handicap index) was 14/60 (functional subscale: 9/20; physical subscale: 2/20; emotional subscale: 3/20) reflecting an increased functional impact of the speech disorder on the quality of life.

Voice

Flexible videolaryngoscopy showed the absence of organic or functional voice disorders. The vocal quality, based on 100% consensus auditory-perceptual evaluation yielded G0 R0 B0 A0 S0 I0, normal pitch and intensity, a DSI value of + 3.9 (MPT: 18 sec, F-high: 694 Hz, I-low: 55 dB, jitter: 0.29%) and a VHI score of 18/120 reflecting the absence of any psychosocial impact of possible vocal problems.

Resonance

The flexible naso-endoscopic evaluation of the velopharyngeal mechanism revealed an adequate lifting of the soft palate with lateral pharyngeal wall constriction during the production of the vowel /a/ and during spontaneous speech (100% consensus evaluation, HV, KVL). The fistula located between the hard and the soft palate was still present. The consensus perceptual evaluation of resonance (100% consensus) revealed the presence of a moderate hypernasality during the production of words and sentences. Nasalance values for the oronasal/oral passage (47%/43%) fell outside the 95% prediction interval.

Articulation

The patient was able to produce all Dutch vowels and all Dutch consonants. The phonetic analysis revealed distortions (labiodental production) of the bilabials /p/, /b/ and /m/ (100%) and a sigmatism simplex (the production of the /s/

sound without sufficient frication in 12 out of 15 instances, i.e. 80%, 100% consensus evaluation). The results of the acoustic analysis are presented in figure 5.1. Figure 5.1 is the F1:F2 scatter plot showing the formant structure of the three corner vowels produced by the patient. The surface of the vowel triangle is 329 kHz^2. This overall result can be further defined by analyzing vowel-to-vowel contrasts along the horizontal axis (reflecting frontal-dorsal tongue positioning as measured by F2 frequency) and along the vertical axis (reflecting tongue height and amplitude of concomitant mandibular movements as measured by F1 frequency). The results are 1366 Hz for the /i-u/ F2 contrast, 494 Hz for the /a-i/ F1contrast and 478 for the /a-u/ F1 contrast.

Oromyofunctional behavior

The consensus perceptual evaluation revealed a decreased lip function in the following functional positions: lip position at rest, dispersion of the corners of the mouth (especially the left corner), lip strength and lip position during swallowing. Complete lip closure was impossible. All tongue functions were normal except the left lateral tongue movement was decreased. Blowing and sucking were still impossible. A decreased function of the lips during swallowing was observed, but drooling was absent.

The total score of the OHIP-14 and its seven constituent are shown in table 5.3. The functional limitation subtest yielded the highest sub-score namely 5. According to the patient, speech problems were effectively related to his teeth (question 1 of the OHIP). The overall satisfaction with the teeth was 87%.

Discussion

The purpose of the present study was to document the speech outcome 12 months after facial transplantation by vascularized composite tissue allotransplantation. Allotransplantation of the face in this patient was considered to restore swallowing, eating and speech and to re-establish aesthetics in a one-stage procedure. No intra- and immediate postoperative complications occurred. A multidisciplinary rehabilitation program started one week postoperatively. Speech rehabilitation was focused on breathing, swallowing, oral motor functions, overall speech intelligibility, voice, resonance and articulation. The speech assessment protocol in this study is focused on every component of speech: voice, resonance, articulation and speech intelligibility. In addition oromyofunctional behavior and facial expressions are examined.

Twelve months after facial transplantation the overall intelligibility is normal in isolated words, but slightly impaired in sentences and spontaneous speech. Intelligibility can be defined as what is understood by the listeners of the phonetic realization of speech. In fact, it is the product of a series of interactive processes. This study focused on three components of speech intelligibility: phonation, resonance and articulation. Taking into account these three components, the authors assume that moderate hypernasality is the main cause of the impaired speech intelligibility. Perceptual vocal characteristics and the objective vocal quality in terms of the DSI are normal. Articulation is characterized by the presence of phonetic disorders (labiodental production of bilabials and sigmatism simplex). This type of phonetic disorders typically have no drastic effect on overall speech intelligibility because they do not disturb the fundamental organization of a language's sound system. Regarding resonance, the patient has a moderate hypernasality during the production of isolated words, sentences and spontaneous speech. Moreover the nasalance values for sounds and for the reading passage fell outside the 95% prediction interval, again reflecting the presence of hypernasality. Since the function of the velopharyngeal mechanism is normal, the presence of hypernasality is related to the fistula located between the hard and the soft palate. The outcome of the vowel formant analyses revealed normal results, despite the presence of increased nasalance values during the production of vowels /a/, /i/ and /u/. Indeed, nasal resonance rather interferes with formant bandwidth than with formant frequencies. The fact that most formant frequency contrast values were slightly better than typical values may be due to the fact that the patient produced sustained vowels. In the context of other sounds, co-articulation occurs during the production of any speech sound, often resulting in a tendency towards higher articulation rates and hence articulatory neutralization. Since vowel formants in this case derived from isolated vowels, co-articulation effects were absent. Consequently, this might have enhanced formant contrasts to some extent. Also the patient in this study might have used compensatory articulation strategies (for example invisible but nevertheless extra retraction or protrusion of the tongue adding to the frontal-dorsal tongue placement contrast).

Comparison of the functional outcomes of all reported face transplant cases is very difficult because results from objective assessment techniques and consensus perceptual evaluations are not systematically available. In the studies of Devauchelle et al. (3), Dubernard et al. (4), Petruzzo et al. (5), Lantieri et al. (7, 9), Siemionow et al. (8), all face transplant case were able to produce intelligible speech within days (3-5, 7), months (9) or years (8) after surgery. In the face transplant patient of this study the overall speech intelligibility is normal in words but slightly impaired in sentences and spontaneous speech due to the presence of a moderate hypernasality related to the presence of a fistula between the hard and the soft palate. Vocal quality in this face transplant patient is normal and articulation is characterized by the presence of two phonetic disorders. In the studies of Devauchelle et al. (3), and Petruzzo et al. (5), the facilitated articulation of the bilabials /p/ and /b/ was mentioned three months postoperative. In the literature oromyofunctional disorders and especially impossible or decreased lip functions (disturbing blowing, sucking and swallowing) are reported. Also in our patient decreased lip functions and lip incompetence in rest, during swallowing and articulation is observed. Drooling was absent. Facial emotional readability was present but decreased. In comparison with the other face transplant patients the functional improvements reflecting emotional facial expression were mentioned 18 months after facial transplantation in the study of Devauchelle et al. (3), Dubernard et al. (4), Petruzzo et al. (5) and two years post-surgery in the study of Siemionow et al. (8). The self-questionnaires in this study reflect the presence of a slight functional disability or slight functional limitation during speech and a very good physical and social well-being without the psychosocial impact of a vocal problem and an overall satisfaction with the teeth. Pretransplant data regarding speech are not available, which is a limitation of this study. These data could have provided a better baseline to evaluate the increase of speech performance and quality of life.

Conclusion

The authors conclude that speech outcome, as one of several determinants of feasibility can be a positive argument when considering the option of facial allotransplantation. It is therefore important to report the functional outcome of this surgical procedure to other facial transplant teams. During the second year of the rehabilitation, the patient in this study will be encouraged to wear the obturator more frequently and for longer periods of time. The facial exercises or mime therapy will focus on further enhancement of facial expression, with the main goal of increasing the functional level of facial muscles (i.e. reduced muscle stiffness and increased facial emotional readability). In addition, speech therapy focusing on articulatory precision for specific consonants and consonant clusters is provided, as well as oromyofunctional training focusing on lip competence. To what extent the combined use of an obturator, the facial exercises and especially the active range of lip movement exercises in combination with the motor-oriented speech therapy can ameliorate the speech intelligibility in this patient is subject for further research.

Disclosure

None of the authors has any financial conflicts of interest in any of the products, devices or drugs mentioned in this article.

Table 5.1: Summary of studies on the functional outcome of facial transplantation cases as found in the literature (M: male, F: female, d: days; m: months; y: years). NA: not available

Surgical team/Authors	**Date**	**Location**	**Recipient Age/sex**	**Allograft**	**Functional outcome**
Devauchelle, et al.[3] Dubernard, et al.[4] Petruzzo, et al.[5]	November 2005	Amiens, France	38,F	Partial myocutaneous	7d:able to eat and drink almost normally 3m:ability to move the upper lip 3m:improvement of lip closure facilitated production of /p,b/ 6m: complete labial contact 6m: phonation and mastication continued to improve, with normal mobilization of the food bolus at 6 months 12m:leakage of drinks from the mouth disappeared 18m: symmetrical smile; functional improvements are reflected in the emotional expressions of the patient's face (feelings of joy or sadness) 5y:blowing, chewing and swallowing is possible, pouting and kissing are still difficult, can talk easily and intelligible
Guo, et al.[6]	April 2006	Xi'an, China	30,M	Partial osteomyocutaneous	2y: able to eat, drink and talk 2y: no complete and symmetrical smile Died at 27 months
Lantieri, et al.[7]	January 2007	Paris, France	29,M	Partial myocutaneous	10d: able to speak and eat
Siemionow, et al.[8]	December 2008	Cleveland, USA	45,F	Partial osteomyocutaneous	2y: regained most of missing facial functions of nasal breathing, sense of smell, drinking from a cup, eating solid foods, and speaking intelligible
Lantieri, et al.[9]	March 2009	Paris, France	27,M	Partial osteomyocutaneous	8m: complete mouth closure 8m: intelligible speech
Lantieri, et al.[9]	April 2009	Paris, France	37,M	Total myocutaneous	NA Died at two months
Pomahac, et al.[10]	April 2009	Boston, USA	59,M	Partial osteomyocutaneous	Ability to breath and speech improved immediately 12 m: unable to pucker lips

Cavadas, et al. [11]	August 2009	Valencia, Spain	42,M	Partial osteomyocutaneous	16m: swallowing and starting phonation rehabilitation
Lantieri, et al. [9]	August 2009	Paris, France	33,M	Partial osteomyocutaneous	8-12m: complete mouth closure 10-24d: recovered intelligible speech
Devauchelle, et al. [3], Dubernard, et al. [4]	November 2009	Amiens, France	27,M	Partial osteomyocutaneous	NA
Gomez-Cia, et al. [12]	January 2010	Seville, Spain	35,M	Partial osteomyocutaneous	NA
Barret, et al. [13]	March 2010	Barcelona,Spain	31,M	Total osteomyocutaneous	4m: unrestricted masticatory movement
Lantieri, et al. [7,9]	June 2010	Paris, France	35,M	Total myocutaneous	NA
Pomahac, et al. [14]	March 2011	Boston, USA	25,M	Total myocutaneous	4m: movement of right-sided muscle groups
Pomahac, et al. [14]	April 2011	Boston, USA	30,M	Total myocutaneous	3m: return of gross lip motion
Lantieri, et al. [7,9]	April 2011	Paris, France	45,M	Partial osteomyocutaneous	NA
Lantieri, et al. [7,9]	April 2011	Paris, France	41,M	Partial osteomyocutaneous	NA
Pomahac, et al. [14]	May 2011	Boston, USA	57,F	Total osteomyocutaneous	3m: no return of motor function
Ozkan et al.[2]	January 2012	Antalya, Turkey	19,M	Total osteomyocutaneous	NA
Blondeel, et al. [15]	December 2011	Gent, Belgium	56, M	Partial osteomyocutaneous	Functional outcome is the purpose of this study
Nasir et al.[2]	January 2012	Ankara, Turkey	25,M	NA	NA
Rodriguez et al.[2]	March 2012	Baltimore, USA	37,M	Total osteomyocutaneous	NA

Table 5.2: Results (and reference data) of the assessments of speech and oromyofunctional behavior 12 months after the facial transplantation.* indicates a value outside the 95% prediction-interval.

	Results of the patient with the facial transplant	Reference data
Speech intelligibility		
Consensus perceptual evaluation		
Words	0: normal	0
Sentences	1: slightly impaired*	0
Spontaneous speech	1: slightly impaired*	0
Speech handicap Index	14/60*	5 /range: 4-6 (normal speakers)[17] 26/range 21-30 (dysarthria patients)[17]
Voice		
Voice Handicap Index	18/120	<20 no disabilities[19]
Consensus perceptual evaluation		
Vocal quality	G0 R0 B0 A0 S0	G0 R0 B0 A0 S0[18]
Aerodynamic measurement		
Maximum Phonation Time (seconds)	18	21.8 (range:6.7-37)[23]
Vocal range		
Softest intensity (dB)	55	51.2 (range: 46-57)[23]
Loudest intensity (dB)	100	96.5 (range: 81-112)[23]
Lowest frequency (Hz)	135	142 (range:96-188)[23]
Highest frequency (Hz)	694	867 (range:453-1282)[23]
Acoustic analysis		
Fundamental frequency (Hz)	121.5	122 (range: 78-166)[23]
Jitter	0.29	0.81 (range: 0-2.1)[23]
Dysphonia Severity Index	+ 3.9	+ 2.5 (range: -5 - +5)[20]
Resonance		
Consensus perceptual evaluation		
Hypernasality	2*	0
Nasal emission	0	0
Nasalance values		
Vowel /a/ (%)	25	20.3 (range: 0-49)[24]
Vowel /i/ (%)	61*	25.8 (range: 0-55)[24]
Vowel /u/ (%)	37*	9.4 (range: 0-24)[24]
Oronasal passage (%)	47*	34 (range: 23-45)[24]
Oral passage (%)	43*	11 (range: 2.5-20)[24]
Articulation		
Consensus perceptual evaluation		
Phonetic inventory	22/22	22/22
Phonetic analysis	Labiodental bilabials /p,b,m/* Sigmatism simplex*	No phonetic disorders
Vowel triangle		
F1 frequency (tongue height + mandibular movements (Hz)		
for /a-i/ F1 contrast	494	minimum 407[25]
for /a-u/ F1 contrast	478	minimum 456[25]
F2 frequency (frontal-dorsal tongue position) for /i-u/ F2 contrast (Hz)	1366	minimum 1193[25]
Surface vowel triangle (kHz^2)	329	minimum 260[25]
Oromyofunctional behavior		
Consensus perceptual evaluation		
Lip function		
Lip position at rest	1*	0
Lip closure	2*	0
Dispersion of the corners of the mouth	1*	0
Lip protrusion	1*	0
Lip strength	1*	0
Lip position during swallowing	1*	0

Tongue function		
Tongue position at rest	0	0
Tongue protrusion	0	0
Tongue retraction	0	0
Tongue lifting	0	0
Tongue depression	0	0
Lateral tongue movements	1*	0
Tongue position during swallowing	0	0
Blowing	2*	0
Sucking	2*	0
Swallowing	1*	0
Presence of drooling	0	0
Facial emotional readability	1*	0
Oral Health Impact Profile		
Total score	13/56*	0/56[21]
Overall satisfaction (%)	87	100% reflecting complete satisfaction[21]
Facial Disability Index		0%completely not satisfied[21]
Physical function (%)	85	100%[22]
Social/well-being function (%)	95	100%[22]

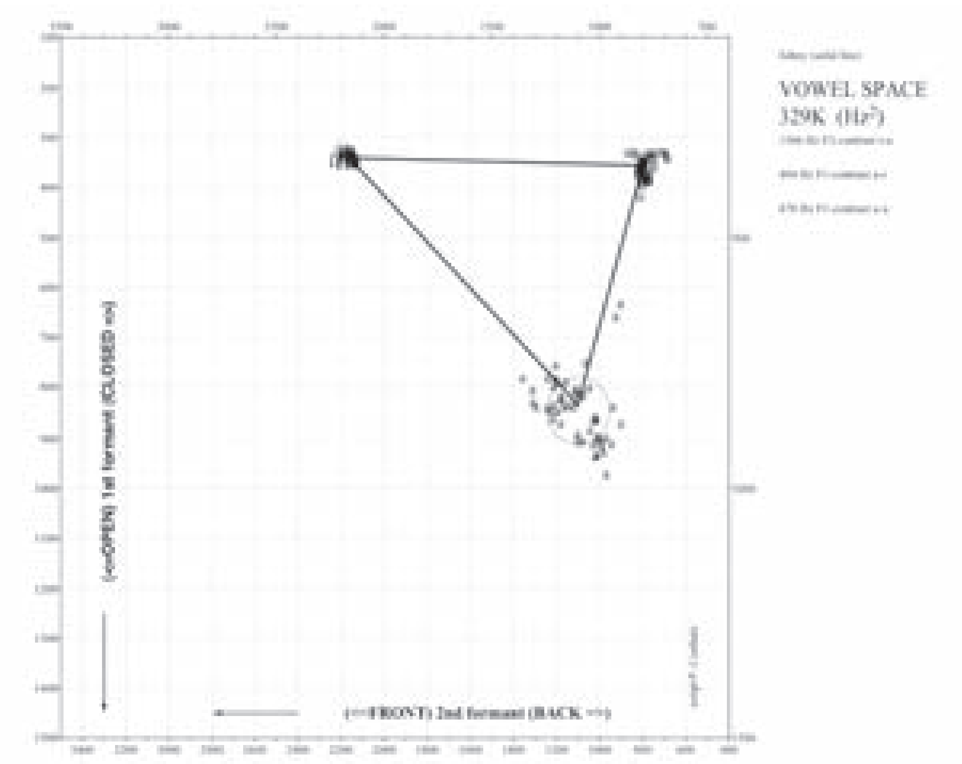

Figure 5.1: F1:F2 diagram of the vowels /a/, /i/, and /u/ produced by the patient. Each vowel symbol corresponds to one time frame in the acoustic analysis. The triangle corners correspond to the 50th percentile of all values. The vertical axis (with F1 frequencies) is the acoustical correlate of mouth opening and tongue height. The abcissa (with F2 frequencies) is the acoustical correlate of tongue position along the frontal-dorsal dimension.

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CHAPTER 6

Longitudinal progress of overall intelligibility, voice, resonance, articulation and oromyofunctional behavior during the first 21 months after Belgian facial transplantation

Based on:

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Abstract

Purpose: The purpose of this study is to document the longitudinal progress of speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior in a male face transplant patient 8 days, 15 days, 5 months, 12 months and, finally, 21 months after surgery.

Method: Identical objective (Dysphonia Severity Index, nasometry, acoustic analysis) and subjective (consensus perceptual evaluation, Dutch speech intelligibility test; flexible videolaryngostroboscopy/naso-endoscopy) assessment techniques and questionnaires (speech and voice handicap index, oral health impact profile, facial disability index) were used during each of the five postsurgical assessments.

Results: The pattern of results shows a longitudinal progress of speech intelligibility and acceptability and of the interactive processes underpinning overall speech intelligibility. Vocal quality is normal and resonance is characterized by hypernasality. The phonetic inventory is complete but four phonetic disorders remain. Outcomes pertaining to articulation (formant analysis) show evident progress over time. Lip functions are improving but still decreased.

Conclusions: Transplantation of the face in this patient has largely restored speech. To what extent resonance, articulation, and lip functions can be enhanced by the permanent use of a palatal obturator, by specialized facial and lip movement exercises in combination with motor-oriented speech therapy, is subject for further research.

Highlights

- This study examines the longitudinal progress of speech in a Face Transplant (FT) patient in 5 postoperative moments
- Transplantation of the face showed a progress of speech intelligibility and acceptability and all the interactive processes underpinning overall speech intelligibility
- Disordered phonetic production of the bilabials is still present 21 months after FT surgery
- Formant analysis showed evident progress over time

Introduction

Since 2005 34 facial transplants were performed (1 - 18). In most cases the surgical, immunological and functional (i.e. swallowing, eating and lip movements) outcomes are very well described. However, very few authors reported detailed analyses regarding the progress of overall intelligibility, voice, resonance, articulation and oromyofunctional behavior after facial transplantation (FT). Only in the report of Devauchelle et al. (3), progress of lip function, swallowing, and articulation was mentioned. In this 38-year-old female patient, a partial myocutaneous face transplantation (FT) was performed in 2005 in Amiens, France. On postoperative day seven the FT patient was able to eat and drink almost normally, and three months postoperatively she had the ability to move the upper lip and to articulate the bilabials /p//b/ with increased lip closure. Six months postoperatively, complete labial contact was observed as well as mastication allowing normal mobilization of the food bolus. Also, phonation continued to improve. Leakage of drinks from the mouth disappeared 12 months postoperatively. After 18 months, facial functional improvements resulted in reflections of emotional expression in the patient's face, allowing her to produce a symmetrical smile. Five years postoperatively blowing, chewing and swallowing were possible and the patient could speak easily and intelligibly. Pouting and kissing were still difficult. Detailed analysis regarding specific voice, resonance and articulation characteristics, although worthwhile knowing, was not provided.

It still needs to be fully determined to what extent the speech characteristics in se can improve after FT. It is known that achieving close relationships with others and developing a positive identity are associated with a subject's ability to communicate well with others (19). Based on the available reports of the first FT patient, a substantial improvement of speech acceptability, speech intelligibility and the involved interactive processes (voice, resonance, articulation) can be expected. The purpose of this study is to document the longitudinal progress of speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior in a male FT patient 8 days, 15 days, 5 months, 12 months and, finally, 21 months after surgery.

Methods and materials

This research was approved by the Ethics Committee (2012/809) of the Ghent University Hospital. Identical objective and subjective assessment techniques and questionnaires were used 8 and 16 days, 5, 12 and 21 months after facial transplantation to determine speech characteristics (speech intelligibility, speech acceptability, voice, resonance and articulation) and oromyofunctional behavior. All techniques have been described in detail in Chapter 5 of this thesis. The speech assessments were performed independently by two speech pathologists (KVL, MDL) who were not involved in the daily speech training sessions.

Subject

The subject was a 54-year-old man, who was admitted to the emergency department in December 2010 due to a ballistic injury to the face. The preparations of the surgery, the surgical procedure, the immunosuppressive induction protocol, surgical results and postoperative complications have been described in detail in chapter 4 of this thesis.

The patient was able to swallow liquids and to produce vowel speech six days after the transplantation. Speech rehabilitation started one week postoperative, 4 to 5 times per week during the first three months and focused on breathing, swallowing, oral motor functions, overall speech intelligibility, voice, resonance and articulation of phonemes, syllables, words and short sentences (20). After three months the frequency of therapy sessions was reduced to 3 times per week. The patient was intrinsically motivated to follow speech therapy and his partner functioned as a co-therapist (21). During logopaedic therapy sessions, the patient was given corrective feedback after every assignment to improve or correct specific productions, using auditory-verbal instructions as well as tactile stimuli. Positive reinforcement was given after every correct attempt and simple yes/no questions were asked, encouraging the patient to comment on his own performance. Also tactile recognition of the facial structures and facial massage were initiated, together with low-vision training. A fistula located between the hard and the soft palate was responsible for a moderate degree of hypernasality (i.e. excess resonance of vowels and voiced consonants within the nasal cavities). An obturator prosthesis was developed to restore the anatomical structures between the oral and nasal cavity. Pure-tone testing revealed normal hearing sensitivity in both ears. Sensory-motor recovery started 4 months postoperatively. Sensory recovery started with restoration of sensations in the oral mucosa and sensations caused by gently touching the chin or one of both cheeks. Recovery of heat and cold sensation started 6 months postoperative. Movements of mouth corners and cheeks and lifting of the nose started 8 months postoperative.

Methods and materials

Speech intelligibility

Speech intelligibility was assessed and analyzed using the Dutch intelligibility test (NVSO = Nederlands Spraak Verstaanbaarheidsonderzoek) and the Speech Handicap Index (SHI) (22, 23) by two experienced speech pathologist (KVL, MDL) using the symbols and diacritics of the International Phonetic Alphabet.

Speech acceptability

Intelligibility and acceptability of speech are different concepts. Dagenais, Brown and Moore (24) described acceptability as the answer to the question, "How would you rate this person's speaking ability?" thus emphasizing the notion that speakers might be able to make themselves intelligible, but at the expense of naturalness, marking their speech as atypical but along different parameters from unintelligible speech. To judge speech acceptability (consensus evaluation by KVL, MDL), a four level ordinal scale was used (0= normal speech acceptability, 1= slightly, 2= moderately and 3= severely impaired speech acceptability).

Voice

Voice assessment (subjective and objective) was performed using flexible videolaryngostroboscopy, consensus perceptual rating based on the GRBASI-scale (G=overall grade of vocal pathology, R=roughness, B=breathiness, A=asthenicity, S=strain and I=instability of the voice), Voice Handicap Index (VHI), aerodynamic measurements, acoustic analysis and Dysphonia Severity Index (DSI)(25 - 28).

Resonance

Resonance assessment (subjective and objective) was evaluated using flexible naso-endoscopy, hypernasality and nasal emission test and measurements of nasalance values (27, 29).

Articulation

Subjective assessment: Speech samples for the assessment of articulation were elicited by means of a picture-repeating test as described in Chapter 5.

Objective assessment: To describe the quality of vowel production an objective acoustic analysis of formant frequencies was used. The first two formants (F1 and F2) are considered to be the most important because, based on those two formants, a listener will be able to identify a given vowel. Determination of F1 and F2 frequencies of vowels offers the possibility to describe vowels in terms of high/low and front/back placement of the tongue in the oral cavity and in terms of jaw opening. Also, the effect of lip protrusion is reflected in the frequencies of both formants in that rounded vowels have an overall lower formant structure. The vowels /a/, /i/ and /u/ represent the extreme articulatory positions of the tongue in English as well as in Dutch. An F1:F2 scatterplot of these vowels yields a so-called 'vowel triangle', i.e. a graphic representation of the articulation space for vowel production with /a/, /i/ and /u/ as 'corner vowels'. Vowel space, i.e. the surface of the scatterplot shape, is a well-known metric that is often used to objectively describe the degree of articulatory precision. When producing a single vowel, a speaker can concentrate on motor actions per se, to demonstrate maximum motor capabilities. Articulatory maneuvers to produce vowels in a phonetic context, on the other hand, reflect a speaker's ability to deal with neutralization and co-articulation. Neutralization pertains to the decrease of movement amplitudes, proportional to speaking rate. Co-articulation is the inevitable mutual influence of movements needed for neighboring segments in connected speech. Both neutralization and co-articulation are related to intelligibility. In this study, both isolated vowels and vowels in context are studied. Isolated /a/, /i/ and /u/ vowels were recorded digitally in a sound booth in Ghent University. Midvowel fragments with stable formant patterns were selected (using visual inspection of the oscillogram and the spectrogram) by means of Praat software (30). These fragments had durations between 500 msec and 800 msec. In addition to isolated vowel samples, [i], [a] and [u] samples were also drawn from digital recordings of monosyllabic nonsense words (NSVO assessment) using the same apparatus and software. As was the case for isolated vowels, mid-vowel segments were selected on graphical displays and were verified auditorily before extracting them using a Gaussian window. The fragments extracted from monosyllabic words had a typical duration of 100 msec., except for some instances of the vowel [a], which is intrinsically longer and therefore often provided stable formant patterns of 200 msec for extraction. To represent each corner vowel, 3 (for isolated vowels) to 6 (for vowels in monosyllable context) fragments were concatenated. These sound files were and subsequently processed using a Praat script involving the Burg algorithm, in order to identify the 50^{th} percentile values of the first two formants. The 50^{th} percentile was chosen as a metric because it is less influenced by artifacts and outliers. From these formant data, vowel space can be quantified. For vowels in a phonetic context, more specific quantitative indices were derived, including vowel-to-vowel contrasts for the first formant (which is indicative of tongue height and mandibular maneuvers) and the second formant (which is indicative of tongue position in the sagittal plane).

Oromyofunctional assessment

Oromyofunctional behavior was evaluated using the protocol of Lembrechts et al. (31), facial emotional readability scoring, Oral Health Impact Profile (OHIP) and the Facial Disability Index (FDI)(32 - 33).

Results

Table 6.1 offers a synopsis of all outcomes over time, as well as appropriate normative indices to evaluate them.

Speech intelligibility and acceptability

Speech intelligibility (100% consensus evaluations of words, sentences and spontaneous speech) changed from severely impaired (during the first 15 days post-transplant) towards slightly/moderately impaired (5 months postoperative). Twelve and 21 months after transplantation, intelligibility was evaluated as normal in single words and as slightly impaired in sentences and spontaneous speech. Speech intelligibility scores in words increased from 72% resp. 76% during the first 15 days post-operative to 84% resp. 90% during the following 5 months and, from then on, stayed approximately at the same level, i.e. 80% (12 months post-op) and 88% (21 months post-op). Speech intelligibility scores in sentences were not available during the first 15 days post-operative because the patient was not able to produce sentences. One month post-transplantation the production of sentences became possible yielding scores increasing from 77% (1 month post-op) to 93% (21 months post-op).

Speech acceptability (consensus evaluation 100%) changed from severely impaired (first 15 days post-transplant) over moderately impaired (1 and 5 months post-surgery) to slightly impaired (12 and 21 months post-transplantation).

Voice and resonance

At one month at and 5 months postoperative, the VHI showed a psychosocial impact of the vocal problem on the quality of life. However, no psychosocial impact of the vocal problem was perceived immediately postoperative and 1 year after the FT. The perceptual evaluation of the overall grade of vocal pathology changed from moderately impaired (8 days postoperative) over slightly impaired (15 days and 1 month postoperative) to normal (5, 12 and 21 months). During the first month after FT, the voice was rough, breathy, asthenic and strained. One month after FT it was possible to calculate the DSI, yielding values increasing from + 1.4 (1 month postoperative) to + 3.6 (21 months post FT).

The moderate degree hypernasality that was noticed (consensus evaluation 100%) during the first 5 months after FT decreased to slight hypernasality after 12 month. During the Bzoch hypernasality tests, from the first assessment (1 month postoperative) to the last assessment (21 months), all words were produced with hypernasality. No nasal emission was observed (consensus evaluation 100%). Nasalance values changed irregularly during the post-transplant period. The lowest nasalance values for vowels (except for the vowel /a/) as well as for the nasometric passages were obtained 12 months after transplantation. During the last assessment (21 months postoperative) a difference in nasalance values with and without the obturator was measured in all vowels and in the nasometric passages.

Articulation

The phonetic inventory was complete from 1 month postoperative onwards until the last assessment (21 months). An increase of the amount of phonetic distortions was observed (consensus evaluation 100%) in the post-transplant period. Ten phonetic distortions were noticed during the first 15 postoperative days and 6 disorders were observed 1 month after FT. Five, 12 and 21 months after FT 4 phonetic disorders were observed.

Outcomes pertaining to articulation in terms of formant analyses show evident progress over time. In the scatterplots it can be seen that over the course of 21 months, vowel space nearly doubled for both isolated vowels (from 120 to 233 k Hz^2 (see figure 6.1) and vowels within a phonetic context (from 85 to 165 k Hz^2) (see figure 6.2). Figure 6.3 shows that vowel space expansion came gradually, reaching a maximum value 5 months postoperatively, followed by a limited downfall 1 year postoperatively. Typical outcomes for vowels produced in a monosyllable context by in male native speakers of Dutch can be derived from data on 50 normal participants in Pols, Tromp and Plomp (34). According to these reference data, the last vowel space result registered 21 months postoperatively comes very close to the lower boundary of the +/- 1 standard deviation bracket. Since vowel space is a composite index, discrete vowel to-vowel contrasts should also be inspected. These vowel-to-vowel contrasts are illustrated by the intervals along the vertical and horizontal scatterplot axes and precise values are given in figures 6.4 and 6.5. There is a different progress rate, depending on the type of articulatory maneuver. The F1 [a-i] contrast (governed by differential tongue height and jaw opening for [i] versus [a]) falls within the +/- 1 standard deviation bracket from 15 days postoperatively onwards. Vowel-to-vowel contrasts where the rounded vowel [u] is involved grow less. As to the F1 [a-u] contrast, only the 5 months and 12 months postoperative values fall within the +/- 1 standard deviation bracket. The only outcome for the F2 [i-u] contrast (governed by differential tongue position in the sagittal plane and by lip protrusion) within the 1 standard deviation bracket normal mean is at 21 months postoperatively.

Oromyofunctional assessment

The consensus perceptual evaluation (95%) revealed an inability to move the lips during the first postoperative month. Five months after FT lip position at

rest, dispersion of the corners of the mouth and lip protrusion became possible, albeit in a reduced manner. Twelve months after FT all lip functions were present but decreased (except for lip closure, which was impossible). During the last assessment at 21 months all lip functions were present, but still decreased.
Perceptual evaluation (95% consensus) revealed a normal tongue position from the first 8 days after FT, but impossible lateral tongue movements and impossible tongue functions during swallowing. Five months after FT all tongue functions were present except for lateral tongue movements, which were decreased in amplitude. During the last two assessments (12 and 21 months after FT) all tongue functions were normal. Blowing and sucking were impossible during all assessments. Drooling was absent from 5 months postoperative onwards. Facial emotional readability was present 12 months after FT. The impact of oral health on the QOL generally decreased from 1 month postoperative until 12 months and 21 months after FT. Only at 12 months after FT a slightly worse result on the oral health impact profile was seen. The Facial Disability Index (both the psychological functions and the social well-being functions) showed an improvement 12 months postoperatively.

Discussion

The purpose of this study was to describe the longitudinal progress of several speech characteristics after FT. Transplantation of the face in this patient was expected to restore speech and to re-establish aesthetics in a one-stage procedure. The findings of this study show that, as hypothesized, all speech characteristics in this FT patient improved over time. Very few authors reported detailed analysis of the progress of the different speech characteristics after FT. Comparison of the evolution of speech characteristics in reported facial transplant cases is very difficult, taking into account the uniqueness of each defect. The most detailed description of functional outcome is available for the first FT performed by Devauchelle et al. (3). Five years after transplantation, this patient could smile, chew, swallow, and blow normally, whereas pouting and kissing remained difficult. Moreover, this patient could talk easily and intelligibly. In the reports of Lantieri et al. (7, 8) and Siemionow et al. (15), the patients were reported to be able to speak and to produce intelligible speech.

Our study is unique in that it shows a longitudinal evolution (according to subjective and objective assessment results) of speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior over a period of 21 months after FT. The pattern of results showed progress in acceptability as well as in intelligibility and all the interactive functions underpinning it (voice, resonance, articulation).

In this patient a digitally planned FT was performed, consisting of a large amount of bone together with the soft tissue of the entire lower 2/3rd of the face. As far as speech physiology is concerned, the muscle systems of the vocal tract (supralaryngeal structures) responsible for resonance, articulation and oromyofunctional behavior were involved. The presence of a moderate vocal problem and the decreased DSI value during the first month post transplantation must be regarded as a temporary sequel of the 20-hour surgical procedure. Resonance and articulation are the interactive processes underpinning speech intelligibility and acceptability. Both the resonance and articulation characteristics continued to improve in the postsurgical period until the last assessment. The phonetic inventory was complete 1 month after transplantation and only four phonetic disorders (disordered bilabials /p,b,m,w/) remained after 21 months. For the production of plosives a certain intra-oral pressure (hypertonic lip seal) is needed. Most likely, there is a causal relationship between the persistency of these phonetic disorders on the one hand and on the other hand the improving but still reduced lip functions. Detailed acoustic analysis of vowel articulation revealed that vowel space expansion was more prominent for isolated vowels. Isolated vowel data reflect motor actions per se, illustrating maximum motor capabilities and including compensatory maneuvers. When a speaker produces complete words, co-articulation sets in (i.e. interference by articulatory maneuvers needed for preceding or following speech sounds) as well as neutralization (i.e. the tendency to lessen the amplitudes of all articulatory maneuvers with growing speech rate). In the F1 [a-i] and [a-u] contrasts, where control over jaw opening is a common factor, this neutralization effect is limiting progress, particularly in the most recent recordings. On the other hand, faster speech rate can be seen as a sign of improvement in itself.

In this patient, the expansion of both types of vowel space values is due mainly to an upward shift of F2 in [i]. This is the acoustic equivalent of better frontal positioning of the tongue. According to the vowel-to-vowel contrast outcomes where [u] is involved, there is less progress when it comes to dorsal tongue elevation and lip protrusion. In normal speakers, lip protrusion elicits lower first and second formants, shifting the top right corner of the vowel triangle to a more extreme position and enhancing all three vowel-to-vowel contrasts. This effect is limited in this patient, due to difficulties with lip functions, particularly with lip protrusion, which were also observed during oromyofunctional assessments. The evolution seen in vowel space and vowel-to-vowel contrasts roughly corresponds with speech intelligibility outcomes, particularly when evaluated at the word level, and with speech acceptability. In fact, this correspondence can be seen as a validation of the techniques and procedures that were used. The downfall of vowel space and all vowel-to-vowel contrasts one year postoperatively should be seen against the background of a general health issue at the time of the assessments, which was not directly related to the transplantation itself (at twelve months a pulmonary aspergilloma relapsed with clinical symptoms of fever and radiologic progression). The degree of hypernasality lessened in the postsurgical period as was reflected in the perceptual evaluations and the nasalance values. During the second year of rehabilitation, the patient was encouraged to wear the palatal obturator permanently to close the palatal fistula. A decrease of the nasalance values while wearing the palatal obturator was seen (reflecting decreased perceived hypernasality) during the last assessment procedure. The longitudinal improvement of the speech characteristics is also reflected in the SHI, VHI, OHIP and the FDI self-assessment questionnaires. The results demonstrate that the FT patient experienced continuous improvements in specific components of speech. These experiences are corroborated by perceptual observations and objective assessments.

This case-report has limitations. First, pre-transplant data regarding speech are not available. Pre-transplant data could have provided a better baseline to evaluate the longitudinal progress of speech performance after FT. Additionally, the role of tongue/palate interaction was not studied, and recovery of normal lingual dynamics is not assessed. The use of a palatometric system to visualize the articulatory postures between the tongue and the palate could have provided valuable information on the role of tongue/palate interaction during articulation of fricatives and explosives. With this instrument it is possible to see exactly where the tongue is hitting the palate in real-time. However, the instrument and logometrix palatometer software were not available at that time. Another method to study the lingual dynamics is multi-view videofluorography and this was not performed. A third limitation of this study is the lack of interdisciplinary relationships. Other research efforts may focus on the interaction between the progress in speech and improvement in social and psychological functioning.

In conclusion, the pattern of results showed a longitudinal progress of speech acceptability, speech intelligibility and all the interactive speech production processes underpinning it. To what extent resonance and articulation characteristics and lip functions can be enhanced by the permanent use of the palatal obturator, and by specialized facial exercises and lip movement exercises in combination with the motor-oriented speech therapy is subject for further research.

	Results 8 days post-op	**Results 15 days post-op**	**Results 1 month post-op**	**Results 5 months post-op**	**Results 12 months post-op**	**Results 21 months post-op**	**Reference**
Speech intelligibility							
Consensus perc. evaluation							
Words	3	2	1	1	0	0	0
Sentences	NT	3	2	2	1	1	0
Spontaneous speech	NT	3	3	2	1	1	0
Dutch speech intelligibility score							
Words (%)	72	76	84	90	80	88	100
Sentences (%)	NT	NT	77	78	91	93	100
Speech handicap Index	23	15	18	18	14	19	5/range: 4-6
Speech acceptability	3	3	2	2	1	1	0
Voice							
Voice Handicap Index	17	15	26	29	18	11	<20/120 no disabilities
Consensus perceptual evaluation							
Vocal quality	G2R2B1A2S1	G1R1B1A1S0	G1R1B0A0S0	G0R0B0A0S0	G0R0B0A0S0	G0R0B0S0	G0R0B0A0S0
Pitch	1	0	0	0	0	0	0
Intensity	1	0	0	0	0	0	0
Aerodynamic measurement							
Maximum Phonation Time (seconds)	10	15	18	17	18	22	22/range:6.7-37
Vocal range							
Softest intensity (dB)	NT	NT	60	58	55	55	51 (range:46-57)
Loudest intensity (dB)	NT	NT	80	95	100	101	97 (range:81-112)
Lowest frequency (Hz)	NT	NT	146	440	135	82	142 (range:96-188)
Highest frequency (Hz)	NT	NT	493	824	694	670	867 (range:453-1282)
Acoustic analysis							
Fundamental frequency (Hz)	120	120	122	124	122	119	122 (range:78-166)

Jitter	1.76	0.52	0.41	0.37	0.29	0.85	0.81(range:0-2.1)
Dysphonia Severity Index	NT	NT	+1.4	+3.8	+ 3.9	+3.6	+2.5 (range -5 -+5)
Resonance							
Consensus perceptual evaluation							
Hypernasality	3	3	3	3	2	2	0
Nasal emission	0	0	0	0	0	0	0
Bzoch hypernasality test	NT	NT	10/10	10/10	10/10	10/10	0/10
Bzoch nasal emission test	NT	NT	0/10	0/10	0/10	0/10	0/10
Nasalance values	NT	NT	NT				
Vowel /a/ (%)				40	25	27/20*	20(range: 0-49)
Vowel /i/ (%)				22	61	54/26*	26(range: 0-55)
Vowel /u/ (%)				14	37	46/9*	9 (range: 0-24)
Oronasal passage (%)				38	47	48/47*	34 (range: 23-45)
Oral passage (%)				37	43	54/39*	11(range: 2.5-20)
Articulation							
Consensus perceptual evaluation							
Phonetic inventory	12/22	21/22	22/22	22/22	22/22	22/22	22/22
Phonetic analysis (amount and specific consonants distorted)	10 /pbmwszfvtd/	10 /pbmwszfvtd/	6 /pbmwsz/	4 /pbmw/	4 /pbmw/	4 /pbmw/	0
Vowel triangle (vowels in monosyllable context)							
F1 frequency (tongue height + mandibular movements) (Hz)							
for /a-i/ F1 contrast	267	354	411	409	361	322	407(+/-1sd: 294-519)
for /a-u/ F1 contrast	265	342	335	403	371	307	455(+/-1sd: 356-554)
F2 frequency (sagittal tongue position+lip protrusion) (Hz)							
for /i-u/ F2 contrast	637	647	749	970	814	1058	1194(+/-1sd: 987-1401)
Vowel space (kHz^2)	85	112	131	196	147	165	265(+/-1sd: 167-363)

Oromyofunctional behavior							
Consensus perceptual evaluation							
Lip function							
Lip position at rest	2	2	2	1	1	1	0
Lip closure	2	2	2	2	2	1	0
Dispersion of the corners of the mouth	2	2	2	1	1	1	0
Lip protrusion	2	2	2	1	1	1	0
Lip strength	2	2	2	2	1	1	0
Lip position during swallowing	2	2	2	2	1	1	0
Tongue function							
Tongue position at rest	0	0	0	0	0	0	0
Tongue protrusion	1	1	1	0	0	0	0
Tongue retraction	1	0	0	0	0	0	0
Tongue lifting	1	1	0	0	0	0	0
Tongue depression	1	1	0	0	0	0	0
Lateral tongue movements	2	2	2	1	1	0	0
Tongue position during	2	2	1	0	0	0	0
swallowing	2	2	2	2	2	2	0
Blowing	2	2	2	2	2	2	0
Presence of drooling	present	present	present	absent	absent	absent	absent
Sucking	2	2	2	2	1	1	0
Oral Health Impact Profile							
Total score	15/56	15/56	8/56	10/56	13/56	8/56	0/56
Facial Disability Index							
Physical function (%)	30	55	65	56	85	60	100
Social/well-being function (%)	72	72	72	84	95	90	100

Table 6.1: Results (and reference data) of the assessments of speech intelligibility, speech acceptability, voice, resonance, articulation (vowel triangle data based on vowels in monosyllable words) and oromyofunctional behavior 8 days,15 days, 5 months and 12 months and 21 months after facial transplantation. NT indicates not tested at that specific post-operative moment. X/X*: nasalance values without obturator/nasalance values with obturator.

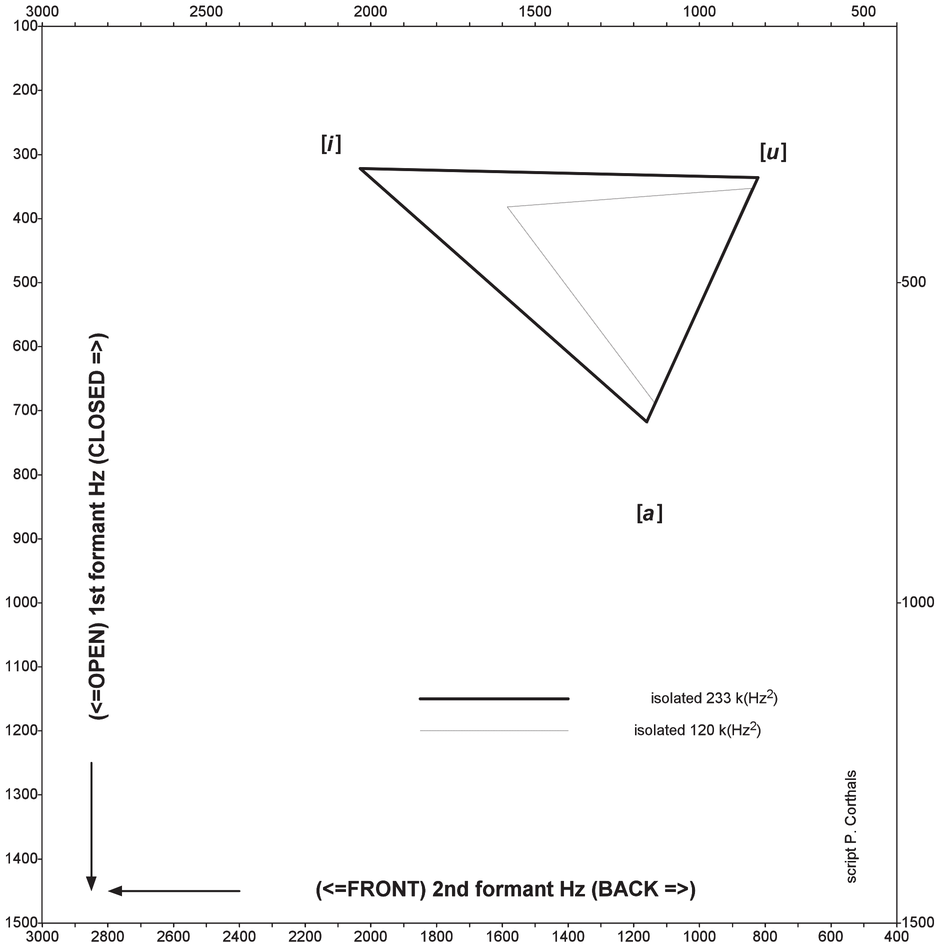

Figure 6.1: F1:F2 scatterplot for sustained corner vowels registered at the start (8 days post operative) and at the end (21 months postoperative) of the study.

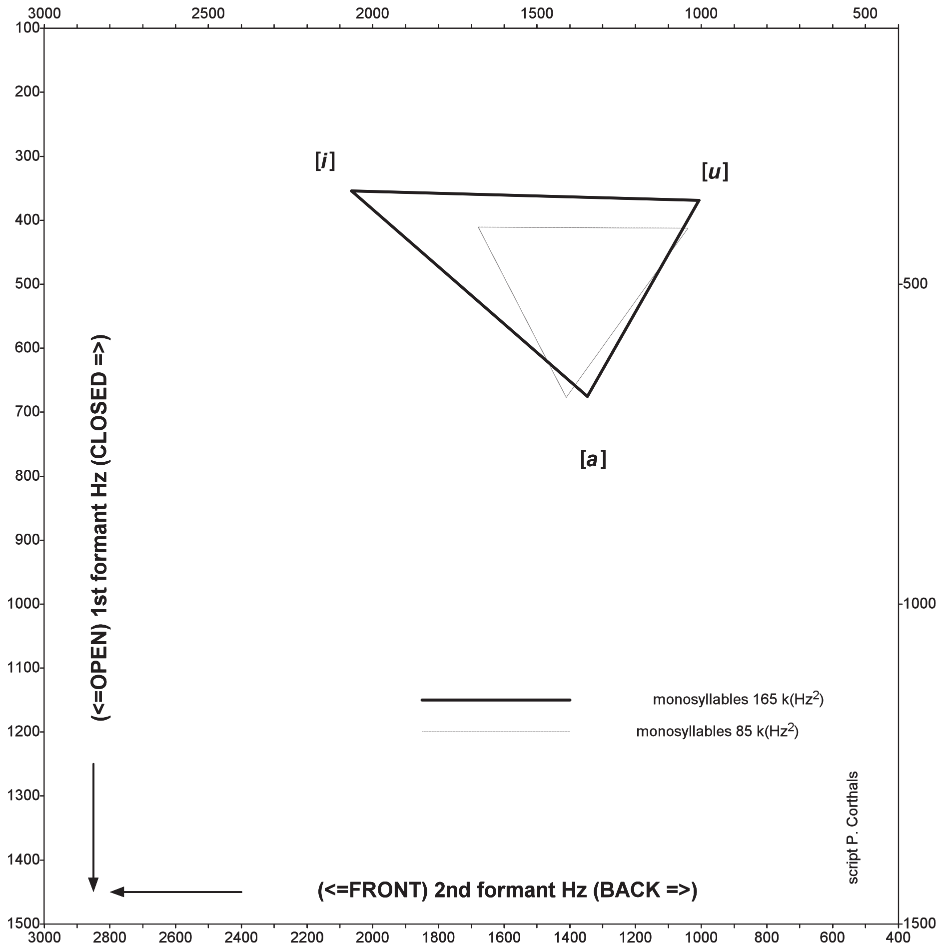

Figure 6.2: F1:F2 scatterplot for corner vowels in monosyllable context registered at the start (8 days postoperative) and at the end (21 months post operative) of the study.

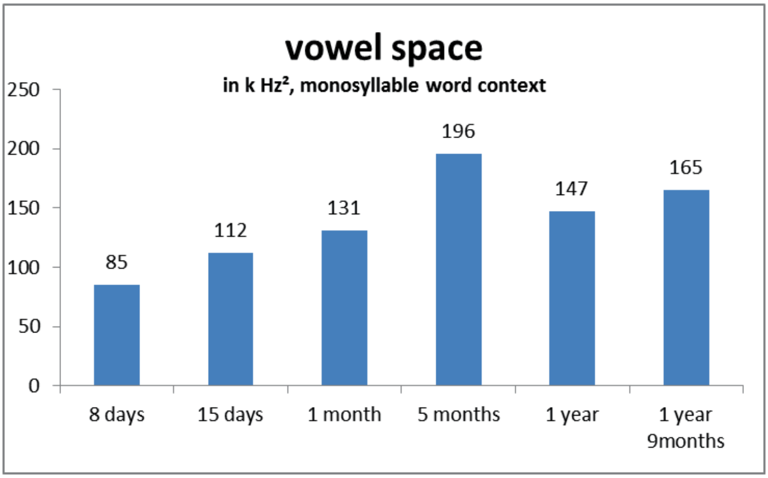

Figure 6.3: Vowel space outcomes in monosyllable context registered at all postoperative assessments.

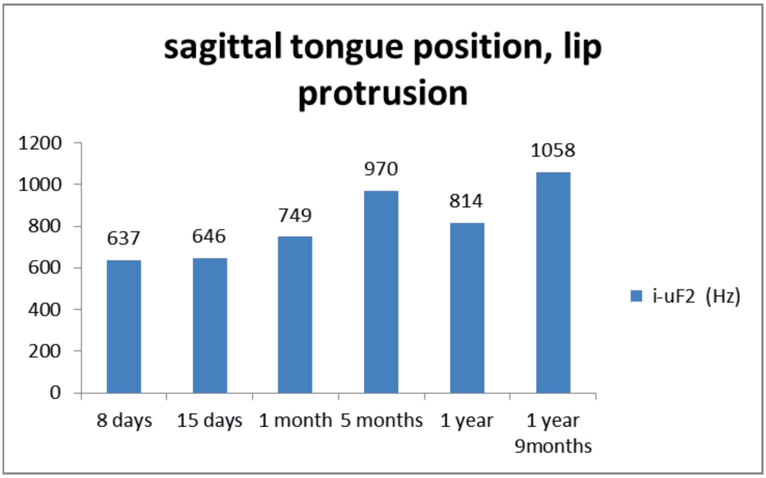

Figure 6.4: Vowel-to-vowel 2nd formant contrasts in monosyllable context registered at all postoperative assessments.

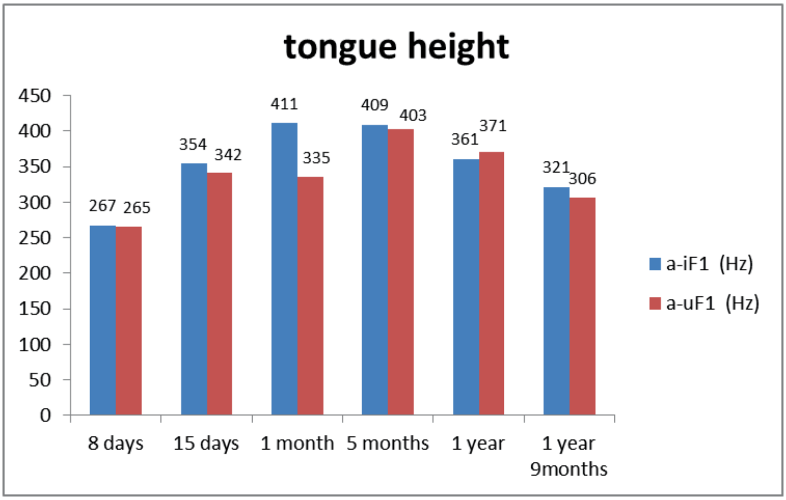

Figure 6.5: Vowel-to-vowel 1st formant contrasts in monosyllable context registered at all postoperative assessments.

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CHAPTER 7

Cortico-muscular recovery in a patient with facial allotransplantation: a 22 months follow-up study

Based on:

De Letter M, Vanhoutte S, Aerts A, Santens P, Vermeersch H, Roche N, Stillaert F, Blondeel P, Van Lierde K. Cortico-muscular recovery in a patient with facial allotransplantation: a 22 months follow-up study. *Brain and Language 2015 submitted*.

Abstract

Introduction: The clinical and neurophysiological evolution of muscular recruitment during speech is followed during a period of two years after facial allotransplantation.

Methods: Sequential electromyography of the lips and contingent negative variation (CNV) during a sentence completion task are used to evaluate axonal recovery and motor preparation. Oral motor function and speech intelligibility were assessed clinically.

Results: A gradual increase of lip EMG amplitude and a reduction of reaction times were found. CNV amplitudes progressively decreased over time. These were paralleled by a global improvement in lip motor function.

Conclusion: Progressive axonal recovery starts early and is accompanied by a gradual decrease in motor preparation effort. Clinically, lip motor function improvement parallels increase of EMG amplitudes, but overall electrophysiological measures seem to be more sensitive indicators of functional recovery.

Key words

Facial Transplantation; Electromyography; Contingent Negative Variation; Reinnervation; Intelligibility; Speech

Introduction

The report of the first face transplantation (FT) in a 38-year-old woman in 2005 (1) launched a decennium of intensive research on FT, with a peak of reports in 2014. Most of the reported patients underwent facial reconstruction after traumatic injury with a complete destruction of the facial nerve. A complete interruption of the neuromuscular pathway from the facial motor nucleus to the facial muscles is accompanied with atrophy and fibrosis of irreversibly paralyzed facial muscles. In contrast to reversibly paralyzed facial muscles which have viable fibers and intact nerve motor units, atrophic and fibrotic facial muscles will not respond to reinnervation until functional muscle fibers replace the damaged tissue, which is the case in FT. The rate of neuronal recovery during the first year after transplantation is assumed to be a predictor of long-term facial nerve recovery (2). Facial muscles that have been completely denervated for less than 1 year would respond to nerve grafting. After 1 year, recovery is variable.

Among the numerous reports on the topic of FT, only 3 report a long-term follow-up on reinnervation of the facial nerve. Lantieri et al. describe a French patient with facial transplantation after resection of a plexiform neurofibroma. Electromyographic examination of the facial musculature was done 3, 6, 9 and 12 months after surgery, with the first registration of electromyographic activity during voluntary contraction after 6 months. Nine months after surgery the patient showed spontaneous mimicry and 12 months postoperatively electromyography displayed signs of motor reinnervation of both trigeminal and facial areas (3). Petruzzo et al., in their first human face transplanted patient, observed motor recovery of the upper lip by the 12th postoperative week (4). Dixon et al. suggest a timeframe between 9-12 months postoperative in which regeneration potentials must be detected in order to consider the nerve transplant as successful (5).

Interestingly, with reinnervation of the facial muscles, cortical mapping not necessarily returns to the pre-injury organization (6, 7). This is an important issue in electromyographic research in patients with complete interruption of the neuromuscular pathway, e.g. in patients with a FT. A frequently used method to measure both reinnervation and cortical mapping is the contingent negative variation (CNV), an event-related potential that can be elicited by a paradigm consisting of a warning and imperative (behavioral) stimulus.

Neuromuscular rehabilitation after nerve grafting is necessary to adjust the appropriate muscles to cortical mapping (8). Currently re-education programs focus on selective muscle control and elimination of synkinesis, an unintentional movement that accompanies a volitional movement, e.g. eyelid closure with mouth movements. The most frequently implemented treatment technique to acquire muscle control is neuromuscular retraining, with or without biofeedback. An electromyogram (EMG) may be performed in order to give real time feedback.

The aim of this study is to describe the process of cortico-muscular recovery for speech output in a patient with facial allotransplantation during a follow-up period of 2 years. Facial neuromuscular recovery, including axonal regeneration, can be estimated using sequential surface EMG. It is hypothesized that peripheral neuromuscular changes will also lead to alterations in processing at a cortical level, reflecting changes in motor preparation and speech effort. Consecutive testing with a CNV paradigm can illustrate such changes. Finally the question is whether changes in one or both of these measures correlate with clinical speech and oromyofunctional recovery. Therefore, sequential testing of myofunctional behavior and intelligibility will be compared with electrophysiological measures.

Materials and methods

Subject

This report describes a 54-year-old man who was admitted to the emergency department of the Ghent University Hospital (Belgium) in December 2010 due to a ballistic injury to the face. He presented with a major soft tissue defect of the lower two thirds of the face and an extensive loss of facial bony structures, including both maxillae and the left half of the mandible. Vision was lost due to bilateral enucleation. Five days after the trauma, a free anterolateral thigh flap was used to temporarily reconstruct the defect. A tracheostomy was required for breathing, as well as a percutaneous gastrostomy tube for feeding. The patient was unable to swallow and speech was unintelligible.

The extensive complexity of the defect and the poor postoperative clinical outcome made it obvious that a conventional reconstructive approach would require multiple extra procedures without guaranteeing an acceptable functional and aesthetic result. Therefore, allotransplantation of the face was considered as an option to restore swallowing, feeding and speech and to re-establish aesthetics in a one-stage procedure. One year after the initial trauma, the patient underwent a digitally planned facial Composite Tissue Allotransplantation (CTA). A detailed description of the preparation of the surgery, the surgical procedure, the immunosuppressive induction protocol and the results of the surgery has been published earlier (9) and has been described in Chapter 4.

No intra-operative surgical complications occurred and the immediate postoperative course was uneventful. The initial presentation of the patient postoperatively was a flaccid facial palsy with muscular atonia, inability to close the eyelids, an absence of the nasolabial fold and a mouth droop. Functionally, the patient was unable to use facial muscles despite maximal effort.

Six days after the transplantation, the patient was able to swallow liquids and to produce vowel speech. Speech rehabilitation started one week postoperatively, 5 times per week (first three months) and focused on breathing, swallowing, oral motor functions, overall speech intelligibility, voice, resonance and articulation of phonemes, syllables, words and short sentences (10).

After three months the frequency of therapy sessions was reduced to three times a week. The patient was very motivated to follow speech therapy, and his partner was functioning as a co-therapist (11). Tactile recognition stimulation of the facial structures and facial massage were initiated together with low-vision training. The patient experienced signs of graft rejection 4 months postoperatively, which was successfully treated with corticosteroids. No further episodes of graft rejection were encountered in the course of the follow-up period. At the final evaluation point of this study, 22 months postoperatively, the patient was treated for an *Aspergillus* infection.

Procedure

In brief, the paradigm that was used consisted of a sentence completion task in which the final word of every sentence was omitted. The sentences were designed so that, based on its content, a particular noun with high probability was evoked (e.g. I eat with knife and ..., The baker bakes …, Every car has four …). As the patient was blind due to enucleation, the sentences were presented auditorily using a conventional binaural headset. This paradigm was used to evoke electromyographic activity of the oral musculature during speech, as well as for the study of cortical electric activity during motor preparation. The procedure was repeated four times in the course of 22 months. The patient was evaluated 1 month, 5 months, 11 months and 22 months postoperatively.

The exact timing of the procedure is depicted in figure 7.1. One hundred sentences were produced by a female speaker and audiotaped in Praat, a free software program for acoustical analysis (Boersma & Weenink, Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands) using a Samsung CU01 microphone (12). To guarantee some equality in duration, sentences shorter than 1700 msec and longer than 3000 msec were deleted. Following this procedure, 91 sentences remained with a mean duration of 2200 (+/- 300) msec and on average i.e.7 .3 (+/- 1.7) syllables. Subsequently, white noise was added at the beginning of each sample, before the sentence was said, in order to create an equal duration of 3000 msec for every sample. In this way, the last word of each sample occurred at the same moment and consequently, the word retrieval process to complete the sentence, started for each sentence approximately at the same time as well.

Following the sentence presentation, a 1000 msec period of silence was included. This period was ended with a click (duration 2-180 msec, mean intensity 76 dB). The patient was instructed to respond with the target word as rapidly as possible after hearing the click. The next sample was started 3000msec after the click. Therefore the total duration of a trial sample (inter-trial interval) was 7000 msec.

Electromyography

For the electromyographic testing, it was important to be able to detect speech onset. Articulatory movements typically precede actual vocalization. Depending on the initial phoneme, the lips or tongue are shown to be the first source (13). Lips are the easiest articulators to detect speech movement onset by use of electromyography (EMG). Therefore, all intended words evoked by the sentence completion task had a bilabial (/m/, /w/, /b/, /p/) or labiodental (/f/, /v/) initial phoneme. If the word was pronounced before the click was given or if the initial phoneme of the word the patient produced was not a labiodental or bilabial, the particular trial was removed from further analyses.

Two electrodes were placed above the right upper and lower lip respectively in order to register bipolar EMG of the orbicularis oris muscle. Lip movement onset was detected by visual inspection of the EMG data of each trial (14 - 16). Therefore, the EMG data were separately band-pass filtered from 15 Hz to 100 Hz to reduce the contamination by motion artefacts and non-myogenic potentials (17). Reaction time (RT) was determined as the time between click onset and lip EMG onset. The amplitude of the EMG of the musculus orbicularis oris was calculated as well. Since even a small alteration in the placement of the electrodes can cause large changes in the amplitude of the EMG signal, its absolute value during speech cannot be compared over several test sessions. It is therefore recommended to use an EMG ratio. Per word, a ratio is calculated between the mean voltage of the EMG during speech and the mean voltage of the EMG during a reference period. The mean EMG during word production is computed from EMG onset to offset because the production of the entire word is relevant. The duration of word production should be comparable over all test sessions. Therefore, only these words that could be included in the RT measurement of *all 4 test-sessions* were included in the EMG amplitude measure. In this way 39 words remained available. Per word, a reference period is also determined. This is a period of inactivity occurring shortly before the word is produced. Since the activity of the orbicularis oris is shown to be inhibited before an imperative signal is presented (18, 19), the best period of inactivity was the 500 msec window before the auditory presentation of the sentence.

Contingent negative variation (CNV)

A CNV paradigm was designed with the auditory presented sentences as warning stimuli (S1) and the click as imperative stimulus (S2).

Continuous electroencephalogram (EEG) was recorded through 20 Ag/AgCl electrodes using a linked earlobe reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10/20 system. These electrodes were located at (pre)frontal (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8), central (C3, Cz, C4), temporal (T3, T5, T4, T6), parietal (P3, Pz, P4) and occipital (O1, Oz) scalp sites. Data were collected in an acoustically and electrically shielded room with the Neuron-Spectrum-5 (4EPM) registration software (Neurosoft, Moscow, Russia) and was continuously digitized at a sampling rate of 500 Hz (0.05-75Hz band-pass filter). Impedance of each electrode was kept below 5 kΩ.

Off-line EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). Data were analyzed with respect to imperative stimulus, leading to stimulus locked analysis.

Since the patient had bilateral enucleation, no eye artefact rejection algorithm needed to be applied. The continuous EEG data were segmented into epochs of 7000 msec, starting 500 msec prior to the warning stimulus (sentence presentation). Similar to the EMG analysis, baseline correction was applied using the first 500 msec of the epochs, prior to sentence presentation, as a reference (20). All trials containing artefacts from drifts, orofacial musculature, swallowing, etc. were manually excluded (21-23). By averaging over corresponding epochs, the CNV potential could be computed for each test moment.

The CNV amplitude was determined by calculating the mean amplitude from the segment between the imperative stimulus (click) and 1000 msec prior to the imperative stimulus for all central electrodes (C3, Cz, C4). This time window was chosen because it contained the maximal variation of the CNV potential.

An additional measure was included because the CNV of the second test session showed a phase inversion. Instead of a negative potential, a very clear positive going deflection could be seen. Consequently, its amplitude contained both positive and negative values neutralizing each other in a mean amplitude measure. Although peak-to-peak amplitude measures may overcome this issue, mean amplitude is generally preferred above peak amplitude measures (20). Therefore, a kind of 'mean to mean' amplitude was calculated in which the difference between the mean amplitude of the first (-1000 to -900 msec) and the last (-100 to 0 msec) 100 msec of the same window was computed.

Statistical analyses

Statistical analyses were performed in IBM SPSS Statistics 19.0. Both RT and amplitude EMG data were separately analyzed for each test using a repeated measures ANOVA with 'test moment' as within-subject factor. Because this factor has more than one degree of freedom in the numerator, Mauchly's Test of

Sphericity was computed to evaluate whether the assumption of homogeneity of covariance was met. If the assumption was violated ($p \leq 0.05$), Greenhouse-Geisser (G-G) adjusted p-values were used to determine significance. Significance values for main effects were set at $p \leq 0.05$. Post hoc comparisons were Bonferroni corrected.

Behavioral measurements

A number of behavioral instruments are feasible for the evaluation of facial nerve paralysis such as the Toronto Facial Grading System (24), the Sunnybrook Facial Nerve Grading System (25) and the House-Brackmann facial grading system (26). Some of these scales are not sensitive enough. Others lack the observation of synkinesis or do not allow the estimation of specific improvement (25, 27). In the selection of the perceptual evaluation scales for the current study, the authors take these considerations into account and therefore opt for the oromyofunctional assessment of Lembrechts, Verschueren, Heulens, Valkenburg and Feenstra (28) and the self-reporting questionnaire Facial Disability Index (FDI) (29).

From the protocol by Lembrechts, Verschueren, Heulens, Valkenburg and Feenstra (28) four topics were assessed: motor lip movement (lip position at rest, lip closure, dispersion of the corners of the mouth, lip protrusion, lip strength, lip position during swallowing), blowing, sucking and the presence of drooling. The sum score of these items results in a composite score for motor lip function. In addition the facial emotional readability (smiling/surprised/sad/angry) was judged for which a three-point rating scale was used (0 = normal function, 1 = decreased function, 2 = function impossible). The above-mentioned speech pathologists (KVL, MDL) first rated independently. In case of disagreement, the samples were replayed and discussed until a consensus was reached.

The Facial Disability Index (FDI) is a reliable and valid self-report questionnaire of physical disability and psychosocial factors related to facial neuromuscular function (29). The FDI can be used as an initial assessment tool and as a monitoring instrument, providing the clinician with the patient's view of the outcome in the intervention progress. The scores on the physical and psychosocial scale are transformed to a 100-point basis (with 100 % reflecting no facial disability).

At each point in time different speech samples were collected in order to judge speech intelligibility at a word and sentence level. For this purpose the protocol of the Dutch Speech Intelligility Test (NSVO - Nederlandstalig Spraakverstaanbaarheidsonderzoek) was used. This is a standardized test which scores intelligibility on a 100% scale, with 100% meaning perfect intelligibility. In the standard test for words the subject is asked to read a list of existing and non-existing words, while the evaluator registers what he/she perceived. These perceptions are compared with the target utterances. By analogy, for the sentence test a written list of semantically meaningless sentences is read aloud by the subject and the evaluator scores the intelligibility likewise. For obvious reasons reading was impossible and repetition of words and sentences was used instead.

Results

Electromyography

At every evaluation moment, the patient was able to attempt utterances of words as rapidly as possible after hearing the click. During the first evaluations EMG amplitude was very low, reflecting the near absence of axonal innervation. The absolute, uncorrected amplitude of the EMG signal, representing labial force, increased in the course of the 22 following months (table 7.1 and figure 7.2).

According to the CNV procedure 80, 76, 72 and 66 words remained in respectively the first, second, third and fourth test moment after rejection of a number of words. The decrease in remaining words within the test moments is due to the increasing number of times the mouth was opened before producing a word (table 7.1). The moments the patient assumes a starting position before speaking leads to a time interval between mouth opening and real word production, which falsely lengthens the RT assessment. However, as explained, further analysis of EMG amplitudes and RT is based on 39 words that could be evaluated in all 4 trial moments.

The RT significantly differed during the performance of the CNV paradigm ($F(1,65)= 235.227$; $\varepsilon= 0.890$; G-G $p\leq 0.001$). A significant decrease in RT was observed when comparing test moment 1 and 2 ($p \leq 0.001$), test moment 2 and 3 ($p = 0.004$), and test moment 3 and 4 ($p \leq 0.001$) (table 7.1).

For EMG amplitude ratio, a significant main effect for the test moment was observed ($F(3,114) = 63.428$; $\varepsilon = 0.572$; G-G $p \leq 0.001$). While the EMG amplitude ratio became significantly smaller when comparing test session 1 with 2 ($p \leq 0.001$), and test session 2 with 3 ($p \leq 0.001$), no significant difference was observed between test session 3 and 4 ($p = 0.08$).

Event-related potentials in the cortex: Contingent negative variation (CNV)

The most pronounced and typical CNV was visible in the first testing (after 1 month, figure 7.3). Further on a decrease in mean amplitude could be demonstrated in all included electrodes, with testing 1 > testing 3 > testing 4. The second testing cannot be compared with the other three because of a phase inversion in the last 1000 msec. The diminution in amplitude can be interpreted as a decrease of effort in the preparation of labial movement in speech in the course of the 22 months postoperatively (figure 7.4a, b).

In view of the interpretation problems due to phase inversion of the CNV 5 months postoperatively, it is difficult to assess correlations between the decreasing amplitudes of the CNV and the increasing amplitudes of the EMG response (see figure 7.5).

Behavioral results

The consensus perceptual evaluation (95%) of the oromyofunctional perceptual evaluation revealed a practically impossible lip function during the first postoperative month. Five months after FT lip position at rest, dispersion of the corners of the mouth and lip protrusion were possible but the function was decreased. Twelve months after FT all lip functions, except lip closure, were present but decreased. During the last assessment at 22 months all lip functions were present but decreased.

Blowing and sucking was impossible during all the assessments. Drooling was absent from 5 months postoperative onwards. Facial emotional readability was present 12 months after FT. The Facial Disability Index (both the psychical functions and the social well-being functions) showed an increase (closer to the reference) 12 months postoperatively.

As expected lip motor function scores seem to correlate best with the increasing EMG amplitudes.
Speech intelligibility for sentences increased steadily over the course of the follow-up period, while intelligibility for words was more variable (figure 7.6). Therefore speech intelligibility for sentences seems to correlate better with the increasing EMG amplitude than word intelligibility (figure 7.6).

Discussion

In the history of human face transplantation we report the earliest facial nerve axonal regeneration (one month) after surgery. A discrete muscle contraction is already electromyographically detectable one month postoperatively, followed by a gradual increasing amplitude of EMG activity in the course of the following months. This increase can be interpreted as an increase of axonal recruitment during lip movement in speech. According to Rivas et al. (2), this early muscle contraction in the initial months can be interpreted as a positive prognostic sign. Significant differences in muscle contraction can be demonstrated between 1 and 5 months, between 5 and 11 months, but not between 11 and 22 months. The lack of significant difference in muscle contraction is probably not a regression of muscle function but a reflection of less overall functioning. It could hypothetically be ascribed to a pulmonary *Aspergilloma* infection with general less well-being. It is also possible that the result at 11 months was already quite good and further improvement was not possible.
A significant decrease in RT is observed when comparing test moment 1 and 2, 2 and 3 and 3 and 4 reflecting less need for preparation time as the recovery progressed. The largest CNV amplitude is visible in the first testing (after 1 month), decreasing in the course of the recovery process, suggesting a decrease in preparation effort when producing speech movements.
Although the oromyofunctional movements are possible but decreased after 22 months, blowing and sucking remain impossible. Drooling disappears after 5 months and facial emotional readability is present 12 months after FT. Interestingly the evolution of the results of the EMG and CNV tests do not agree with the evolution of all perceptual scales. In the first test moment (one month after FT) functional facial movements cannot be detected, while a minor

muscular contraction is already demonstrated with EMG. The fact that regenerating potentials (EMG) can be detected at the time that functional recovery is still absent suggests a higher sensitivity of the EMG than for perceptual measurement. Therefore EMG not only benefits as biofeedback (as an adjunct to reeducation) but also as a diagnostic tool in early investigations of reinnervation. The best clinical correlates of the electromyographical demonstrated axonal regeneration are the motor lip performance of the oromyofunctional perceptual evaluation and the sentence intelligibility score of the Dutch Speech Intelligibility test.

This study stresses the importance of investigating facial recovery with surface EMG in patients with FT. An early detection of muscular contraction with EMG in the recovery process has a positive prognostic value (2) and gives, in combination with CNV paradigms, additional information about motor preparation time needed to achieve speech production. Moreover, this methodology is independent of intrinsic motivation of the patient and interpretation of the investigator, allowing more consistent and objective results over time. Whether the current findings can be transferred to other facial muscles and whether cerebral plasticity, driven by neuromuscular regeneration, influences the recovery of other speech and languages modalities is a matter for future research.

Acknowledgements

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Disclosures

None of the authors has any financial conflicts of interest in any of the products, devices or drugs mentioned in this article.

Evaluation (months postoperatively)	1	5	12	22
Mean EMG amplitude (microvolt)	9	12	32	68
Mean EMG reaction time (msec) (SD)	520 (163)	266 (108)	192 (126)	-85 (93)
Mean CNV amplitudes (microvolt)				
F3	8,5	1,8	5,8	3,5
Fz	10	1,3	6,8	2,9
F4	7,6	-0,9	4,2	2,0
C3	9,2	2,1	5,1	4,0
Cz	9,2	3,0	7,0	4,5
C4	7,9	1,2	4,8	3,1
Oromyofunctional assessment				
Motor lip - composite score (/20)	20	14	12	10
Facial emotional readability (/56)	8	10	13	8
Facial disability index (%)	72	84	95	90
Intelligibility				
NSVO Words (%)	84	90	80	88
NSVO Sentences (%)	77	78	91	93

Table 7.1:

Neurophysiological and behavioral results at all evaluation points.

EMG = electromyography

CNV = contingent negative variation

NSVO = Nederlandstalig Spraakverstaanbaarheidsonderzoek

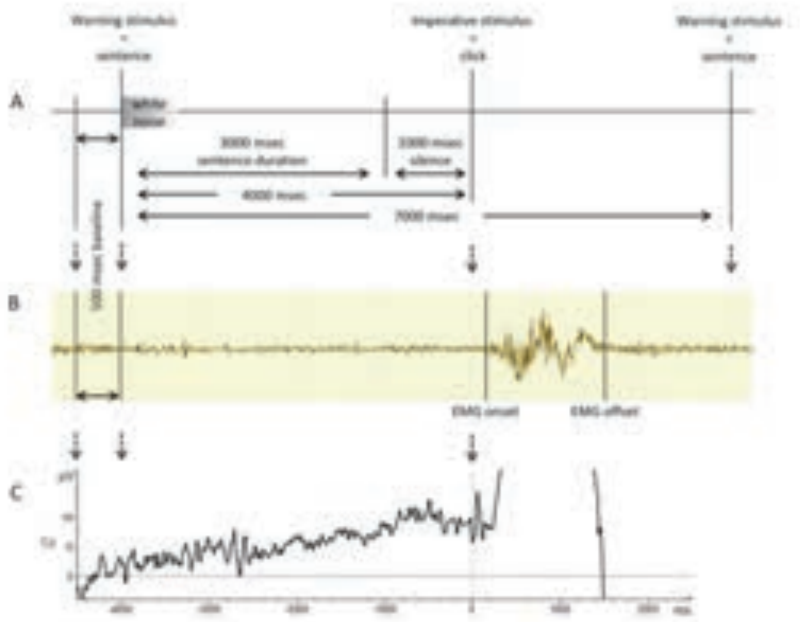

Figure 7.1:

(A) Diagram of the sentence completion CNV task. The warning stimulus (S1) consists of an auditorily presented sentence, the imperative stimulus (S2) of an auditory click to prompt the participant to name the picture as quickly as possible. Interstimulus interval is 4000msec, intertrial interval 7000 msec. The warning stimulus starts with a period of white noise that has a variable duration in order to create an equal duration of 3000 msec for every sample. The last 1000 msec before the imperative stimulus is presented, are silent. (B) EMG signal of the orbicularis oris muscle of one response. The onset and the offset of the EMG signal are marked. Its average voltage is compared to the average voltage of the 500 msec baseline-period to calculate the EMG ratio amplitude. Reaction time is the time between imperative stimulus onset and EMG onset. (C) Stimulus locked average at Cz at the first test session. Latency (x-axis) is represented in milliseconds (msec) and amplitude (y-axis) in microvolts (μV). Negative is plotted upwards. Baseline is the first 500 ms op the epoch i.e. 500 msec before the warning stimulus onset. The 0 msec point is the onset of the imperative stimulus.

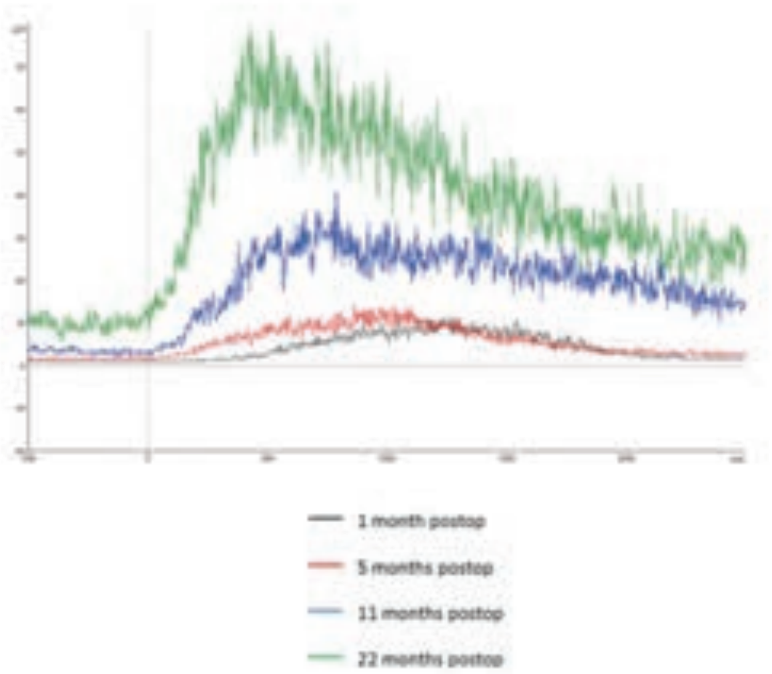

Figure 7.2:

Rectified grand average of the labial EMG responses corresponding with verbal word output at sentence completion. Each curve contains the average of 39 EMG samples, corresponding to the output words that were equal in all trials (see text). Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (μV). A clear increase in amplitude over time is visible, as well as a reduction in reaction time.

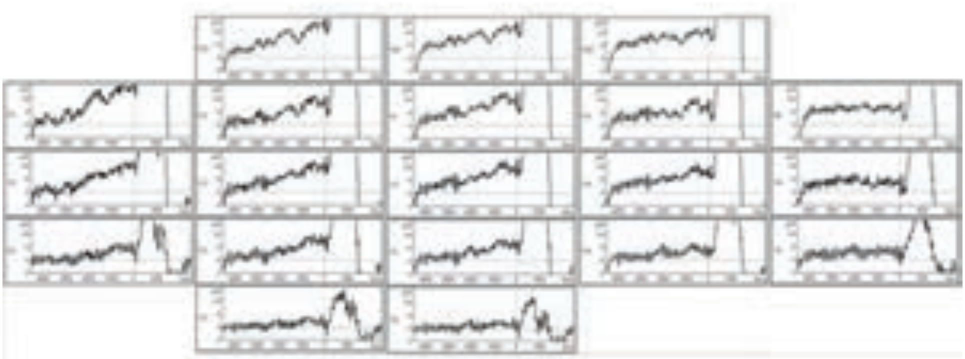

Figure 7.3:

Stimulus locked analysis of all electrodes at the first test session. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (μV). Negative is plotted upwards. Baseline is the first 500 ms of the epoch i.e. 500 ms before the onset of the warning stimulus (sentence). The 0 ms point is the onset of the imperative stimulus (click).

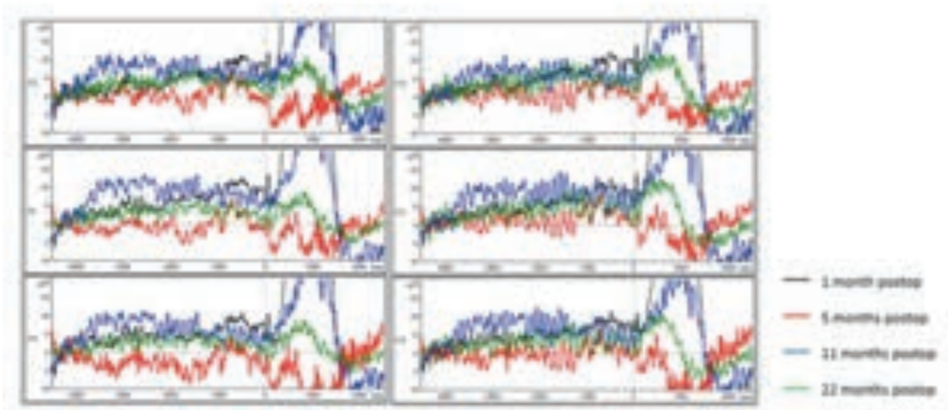

Figure 7.4a:

The CNV after stimulus locked analysis at F3, Fz, F4 (on the left) and C3, Cz, C4 (on the right) for all test sessions. Latency (x-axis) is represented in milliseconds (ms) and amplitude (y-axis) in microvolts (μV). Negative is plotted upwards. Baseline is the first 500 ms of the epoch i.e. 500 ms before the onset of the warning stimulus (sentence). The 0 ms point is the onset of the imperative stimulus (click).

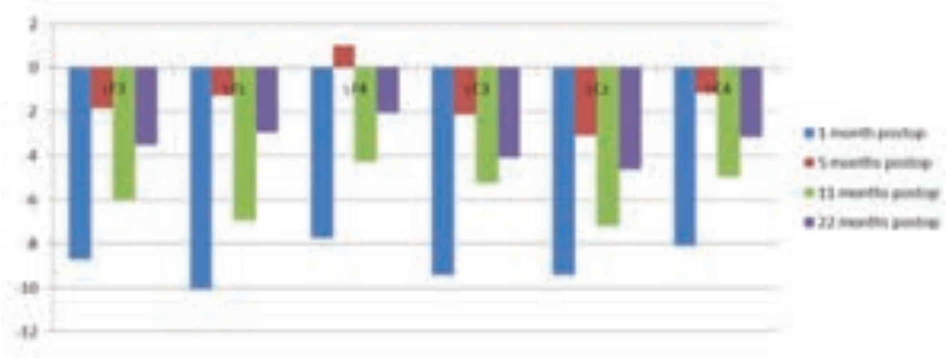

Figure 7.4b:

Diagram presenting the evolution of CNV amplitudes at the central electrodes over time.

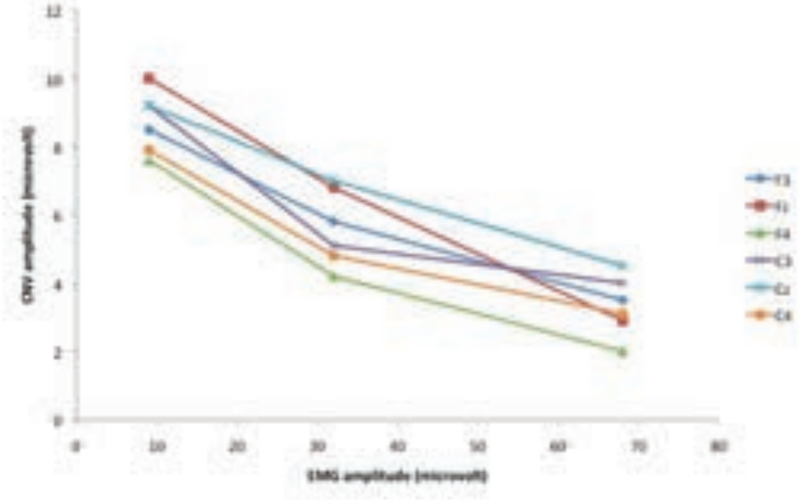

Figure 7.5:

Correlation of labial EMG-amplitude (x-axis) and CNV amplitude at different central electrodes. Both axes are expressed in microvolts. In view of the interpretation problems with CNV amplitude at the second evaluation moment (5 months), these data points were left out.

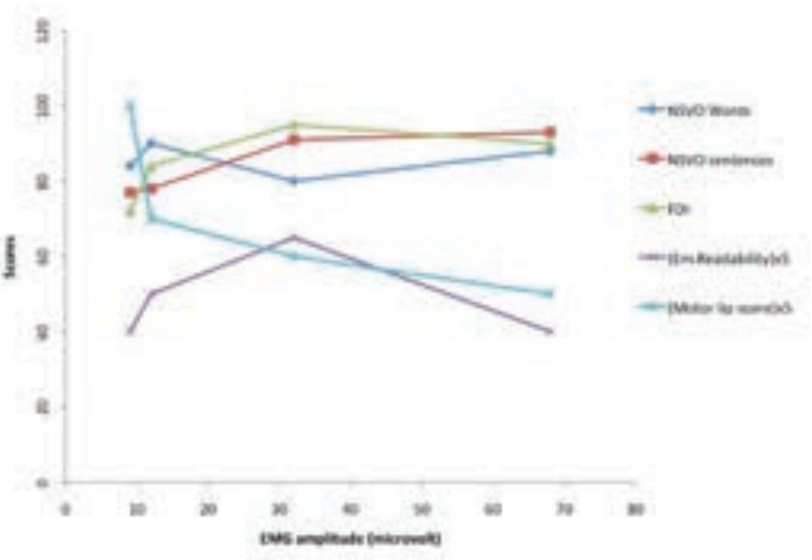

Figure 7.6:

Correlation of labial EMG-amplitude, expressed in microvolts (x-axis) and behavioral measures (scores in Y-axis).

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CHAPTER 8

Facial transplantation in a blind patient: psychological, marital and family outcomes at 15 months follow-up

Based on:

Gilbert MD Lemmens, Carine Poppe, Hannelore Hendrickx, Nathalie A Roche, Patrick C Peeters, Hubert F Vermeersch, Xavier Rogiers, Kristiane Van Lierde, Phillip Blondeel. Facial transplantation in a blind patient: Psychological, marital and family outcomes at 15 months follow-up. *Psychosomatics 2014 doi:10.1016/j.psym.2014.05.002.*

Abstract

Background: Quality of life has frequently been reported to improve after vascularised composite allotransplantation of the face. However, psychosocial functioning of the partner or of particular patient groups such as blind patients are until now less well investigated.

Objective: The aim of this study is to investigate psychological, marital and family functioning of a blind 54-year-old patient and his partner after facial transplantation.

Methods: Depressive and anxiety symptoms, hopelessness, personality, coping, resilience, illness cognitions, marital support, dyadic adjustment, family functioning and quality of life of the patient and the partner were assessed before and after facial transplantation and at 15 months follow-up. Reliable change index (RCI) was further calculated to evaluate the magnitude of change.

Results: Most psychological, marital and family scores of both the patient and the partner were within a normative and healthy range pre- and post-transplant and at 15 months follow-up. Resilience (RCI: 3.6), affective responsiveness (RCI: -3.6), disease benefits (RCI: 2.6) of the patient further improved at 15 months follow-up whereas the physical quality of life (RCI: -14.8) strongly decreased. Only marital support (RCI: -2.1) and depth (RCI: -2.0) of the partner decreased at 15 months.

Conclusions: The results of this study point to positive psychosocial outcomes in a blind patient after facial transplantation. Further, they may underscore the importance of good psychosocial functioning pre-transplantation of both partners and of their involvement in psychological and psychiatric treatment.

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V

Key words

Blind patient; Facial transplantation; Psychosocial functioning; Quality of life

Introduction

The face plays a central role in identity, attractiveness and social interactions. Consequently patients with severe facial disfigurement because of injury or illness may suffer important psychological and social sequelae (1 - 3). Several difficulties such as depression, anxiety, low self-esteem and quality of life, poor marital and social relationships and changes in body image have frequently been reported (3). Moreover, traditional plastic and reconstructive surgery techniques involving multiple surgeries usually offer poor aesthetic and functional outcomes and may cause additional stress and morbidity (4).

Composite tissue allotransplantation of the face has progressed over the past decade from an experimental possibility to a clinical reality for restoring structure and function of patients with extensive facial disfigurement (5 - 7). To date, 34 face transplants have been performed worldwide (8). Reports of the first 18 transplants indicate that facial transplantation is surgically feasible and technically successful (4, 5, 8 - 10). Preliminary psychological findings further point to improved quality of life, less psychological distress and depression, less verbal abuse, good acceptance of the new face and social (re)-integration, though self-esteem may not alter post surgery (8, 11 - 15).

The limited knowledge about long-term outcomes of facial transplantation has complicated the debate about inclusion/exclusion criteria (1, 16 - 20). One area that remains controversial is the issue of blindness (20 - 22). Some authors have declared that complete bilateral blindness should be considered as a contraindication since blind patients may be less able to adequately participate in the therapy required following transplantation and to perform regular self-monitoring for rejection. Further, they may be less affected by social reactions to their disfigurement and may be less able to appreciate the visual aesthetics of the transplant. However, others have argued for their inclusion based on functional, social, rehabilitative and ethical grounds. Pomahac and colleagues (20) have performed full face transplant procedures on two patients with complete bilateral blindness with sensory-motor and psychological recovery consistent with those reported for sighted patients. However, they emphasized the importance of a strong support network for assisting the blind patient pre- and postoperatively.

The aim of this study is to investigate different aspects of psychological, marital and family functioning of a blind patient pre- and post transplantation. Further, since the transplant surgery and recovery may have burdened the partner and the marital relationship (15), psychosocial functioning of the spouse of the facial transplant patient was also examined.

Methods

Participants and selection

A 54-year-old male patient and his female partner (52 years) participated in this study after giving their written informed consent. They have been married for more than 30 years and have several children.

The patient had suffered a ballistic trauma. There was an important loss of central facial tissues, the nose and the maxilla, primarily on the left side, and bilateral blindness. Because of the extensiveness (>2/3) and the complexity of the defect to the central most mobile area of the face and the expected poor clinical outcome with a conventional reconstructive approach, allotransplantation of the face was considered as an option to restore vital functions and re-establish aesthetics in a one-staged procedure.

After extensive screening based on the research protocol developed by Prof. Dr. Laurent Lantieri (CHU Henri Mondor, Créteil/Paris, France) (12) and advice/feedback from international experts (Paris, France and Cleveland, U.S.A.), the patient was considered to be a possible candidate for facial transplantation. Within the original protocol, blindness was never considered as a contra-indication since blind patients should on functional and ethical grounds have equal access to face transplantation. Exclusion criteria for the transplantation were inability to give informed consent, pregnancy and breast feeding, age < 18 years, chronic infections such as HIV, serious somatic illnesses increasing mortality post transplant, smoking, alcohol and substance abuse, schizophrenia and other psychotic disorders and any personality disorder causing important psychological instability. The protocol further prescribed an independent assessment by a psychiatrist and a psychologist before surgery and a regular psychiatric and psychological follow-up up to 5 years post transplant. Pre-transplantation the patient was extensively assessed by a psychiatric team, including a psychiatrist, a psychiatrist in training and two psychologists (of which one was an expert in transplantation psychology). The baseline assessment took place 3 months after the facial trauma and included a psychiatric history, a present state examination, the Mini International Neuropsychiatric interview (MINI, Dutch version 5.0.0, section A to O) (23), and several psychological interviews examining possible contra-indications for the facial transplantation, medical compliance, coping skills, expectations about the outcome and social support.

Baseline assessment of psychiatric illness revealed that the patient only satisfied for a lifetime, not current, depressive disorder. His family psychiatric history was unremarkable. No alcohol and substance abuse/dependency were present. Extensive psychological and psychiatric assessment retained no contra-indications for the transplantation procedure. One year after the facial trauma, the patient underwent facial surgery by a team led by the last author. This study was approved by the Ethics Committee of the University Hospital of Ghent in accordance with the principles of the Declaration of Helsinki.

Assessment

At baseline, both the patient and his partner were asked to complete a battery of self-reports investigating psychological and relational functioning. They included the Beck Depression Inventory II (BDI-II), the Spielberger State Anxiety Inventory (STAI), the Beck Hopelessness Scale (BHS), the Utrecht Coping List (UCL), the Temperament and Character Inventory (TCI), the Dutch Resilience Scale (RS-nl), the Family Assessment Device (FAD), the Dyadic Adjustment Scale (DAS), and the Quality of Relationships Inventory (QRI). The Illness Cognition Questionnaire (ICQ), the 36-item Short Form Health Survey (SF-36) and the MINI psychiatric interview were only completed by the patient. Because of the blindness, the patient was assisted in filling in the questionnaires by a member of the psychiatric team. Questionnaires were re-administered post transplantation and at 15 months post surgery.

Measures

The Beck Depression Inventory II (24, 25) is a 21-item self-report questionnaire assessing the severity of depressive symptoms: 0-13 (minimal), 14-19 (light), 20-28 (moderate) and 29-63 (severe). The BDI-II shows high internal consistency and test-retest validity.

The Spielberger State Anxiety Inventory (26, 27) is a 20-item self-report questionnaire assessing state and trait anxiety. Total scores vary from 20 - 80. For both state and trait anxiety, internal consistency is high. For trait anxiety, test-retest reliability is relatively high, whereas for state anxiety the stability coefficient tends to be low, as expected.

The Beck Hopelessness Scale (28) is a 20-item self-report questionnaire assessing 20 statements about the future that the subject rates as true or false. A score higher than 8 indicates levels of hopelessness associated with an increased risk of suicide. The scale has excellent internal consistency and test-retest reliability.

The Dyadic Adjustment Scale (29, 30) is a 32-item self-report measuring relationship adjustment. Scores (below 100) represent significant relationship dissatisfaction or distress. It yields a total adjustment score and four sub-scores reflecting satisfaction, consensus, cohesion and affectional expression. Psychometric analyses support its test-retest reliability and validity.

The Family Assessment Device (31 - 33) is a 60-item measure assessing family functioning across seven dimensions: problem solving, communication, roles, affective responsiveness, affective involvement, behavior control and general functioning. A higher score on the FAD indicates *poorer* or *unhealthy* family functioning. The scale has good internal consistency and test-retest validity.

The Quality of Relationships Inventory (34 - 36) is a 25-item measure of spousal social support. The instrument includes 3 subscales: support, conflict and depth. The test–retest reliability and internal consistency are both satisfactory.

The Dutch Resilience Scale (37, 38) is a 25-item measure assessing resilience. The instrument is scored on a 7-point Likert scale with a maximum score of 175. It has two components ‘Personal Competence’ and ‘Acceptance of Self and Life’. Test–retest reliability and internal consistency are satisfactory.

The Utrecht Coping List (39) consists of seven subscales, with 47 items, measuring different coping styles in problem situations: active problem solving, palliative reaction, avoidance, socialization, passive reaction, expression of emotions and reassuring thoughts. Internal consistency and test–retest reliability are satisfactory.

The Short Form Health Survey (40, 41) is a 36-item questionnaire consisting of a mental health (vitality, social functioning, role-emotional, and mental health) and a physical health (physical functioning, role-physical, bodily pain, and general health) component. The higher the summary scores, the better the quality of life. The SF-36 is a reliable and valid instrument.

The Illness Cognition Questionnaire (42) is an 18-item Dutch questionnaire measuring three generic illness cognitions that reflect different ways of re-evaluating the inherently aversive character of a chronic condition: acceptance ('a way to diminish the aversive meaning'), helplessness ('a way of emphasizing the aversive meaning of the disease') and disease benefits ('a way of adding a positive meaning to the disease'). Items are scored on a 4-point scale with a maximum score of 24. Test–retest reliability and validity are satisfactory.

The Temperament and Character Inventory (43 - 45) is 240-item, true-false self-questionnaire including 7 dimensions of personality, divided in four temperaments (novelty seeking, harm avoidance, reward dependence and persistence) and three characters (self-directedness, cooperativeness and self-transcendence). The TCI is a reliable and valid instrument.

The SEH ('Subjective Emotional Health) is a 2-item measure assessing the current psychological and emotional state of one-self and the partner: 'How would you describe the current emotional and psychological condition of yourself/ of your partner'. The items are rated on a 4-point Likert scale (1 = poor, 2 = not very good, 3 = quite good, 4 = very good).

Data analyses

Because of the single case design, the changes over time were described. Clinical significant changes were examined in two different ways. First, the results of the patient and the partner were compared with mean non-clinical population scores and/or cut-off scores of the questionnaires when available (46). Secondly, to determine whether the magnitude of change was statistically reliable, the reliable change index (RCI) for each assessment scale was calculated using the formula: RCI= (pretest score-posttest score)/Sdiff. Sdiff is the standard error of difference between the two test scores. An RCI above 1.96 is indicative of statistically reliable (positive or negative) change in N=1 designs (47, 48). RCI of the Illness Cognition Questionnaire was calculated on data from rheumatoid arthritis (RA) population because normal control population data were lacking (42).

Results

Surgical and medical treatment

The preparation of the surgery, the surgical procedure, the immunosuppressive induction and maintenance protocol and the results of the surgery are extensively described elsewhere (49, 50). Several medical complications occurred after the transplantation: an impaired glucose tolerance (month 1), an abscess with *Aspergillus fumigatus* at the proximal mandibular plate (month 3), a grade IV rejection of the graft and a sinusitis due to *Pseudomonas aeruginosa* (week 15), pulmonary nodules suspect for aspergilloma, hyponatremia due to a syndrome of inappropriate secretion of ADH (SIADH) caused by the voriconazole treatment and an asymptomatic cytomegalovirus viremia (month 6), five painful osteoporotic thoracic vertebral fractures (month 7), stupor for two days related to a hyponatremia (116 mmol/L) due to a SIADH caused by the citalopram treatment in combination with fentanyl patches treatment for the fractures pain (month 8), a relapse of pulmonary aspergilloma with a *Pseudomonas aeruginosa* surinfection pneumonia (month 11). As a result, the patient was frequently re-hospitalized (in total for 137 days) during the first 13 months post transplantation. Additionally, when discharged from the hospital, he was also treated on a high frequently outpatient base (between 3-7 hospital visits/week). Between month 13 and 15 the clinical situation remained remarkably stable and only low frequent outpatient treatment was necessary (49, 50).

Pschychological and psychiatric treatment

The transplantation protocol prescribed regular psychological and psychiatric treatment of the patient pre- and post-surgery. Therefore, a weekly consultation with the psychologist and the psychiatrist during admission and one psychological session every fortnight and a monthly psychiatric consultation when discharged from the hospital were organized according to standards of a regular to intensive psychiatric/psychological treatment. In the pre-transplant period 12 psychiatric consultations and 43 psychological consultations (e.g. 17 individual patient sessions, 7 couple sessions, 19 family (member) sessions) were conducted. During the 15 months post surgery period, 35 psychiatric consultations (mainly with the partner) and 4 family member sessions by the psychiatrist took place. Additionally 26 psychological sessions (14 individual patient sessions, 8 couple sessions, 4 family (member) sessions) were performed.

Psychological and marital outcome

Table 8.1 shows the psychological, marital and family functioning of the patient and the partner at baseline, post-surgery and at 15 months follow-up.

Baseline

At baseline both the patient and the partner showed minimal depressive symptoms, mild hopelessness, low state and trait anxiety, high resilience, high marital support, high dyadic adjustment, and healthy family functioning (except for the patient's affective responsiveness subscale). Further, no arguments were found for any personality disorder of the patient and the partner. The coping style of the patient was characterized by high problem solving, low reassuring thoughts and very low expression of emotions whereas the partner reported high problem solving, high palliative reaction and high avoidance, very high socialization, very low expression of emotions and very low passive reaction. Finally, in contrast with his partner who rated the emotional health of the patient as poor, the patient reported a very good subjective emotional health.

Postoperatively and at follow-up

Psychological, marital and family functioning of both patient and partner slightly improved post surgery, but most scores tended to return to pre-transplant levels at follow-up. At follow-up the patient's coping style showed higher palliative reaction (RCI: 2.1) and higher avoidance (RCI: 2.2). Resilience of the partner remained unchanged whereas resilience of the patient (RCI: 3.6), including competence (RCI: 3.9) and acceptation (RCI: 2.1) increased at follow-up. His affective responsiveness improved post-op (RCI: -4.5) and at follow-up (RCI: -3.6) as well as communication at follow-up (RCI: -2.6). Although dyadic adjustment steadily improved, the marital support (RCI: -2.10) and depth (RCI: -2.01) of the partner decreased at follow-up.

The health-related quality of life of the patient improved post surgery, but decreased at 15 months follow. Especially the physical quality of health improved after surgery (RCI: 8.7), but strongly decreased at follow-up (RCI: -14.8). Follow-up scores were about 60% of baseline scores (RCI: -6.1). In contrast with mental quality of health, the physical quality of health score was lower at follow-up compared to the mean score of a healthy population. Further, all illness cognitions strongly improved post surgery: helplessness (RCI: -2.9) decreased, acceptance (RCI: 2.4) improved and disease benefits (RCI: 4.6) increased post surgery, but these changes remained not clinically reliable at follow-up except for disease benefits (RCI: 2.6).

MINI psychiatric interview at 15 months follow-up showed similar results as the baseline interview: a lifetime, not current, depressive disorder. Patient was daily treated with citalopram 40 mg and trazodone 100mg at the baseline assessment until 8 months post transplant.

Discussion

This study has investigated psychological, marital and family outcomes of a blind facial transplant patient and his partner. Although psychosocial functioning of both participants was pre-transplant within a normative and healthy range, most measures, particularly illness cognitions, physical quality of life and affective responsiveness of the patient further improved post surgery. At follow-up, most results returned to pre-transplant levels except for resilience, communication, affective responsiveness, palliative reaction and avoidance of the patient. Only, physical quality of life of the patient and marital support and depth of the partner decreased at 15 months.

Before discussing our findings some limitations to the generalizability of the results need to be addressed. They include the short follow-up, the possible inclusion/selection bias (e.g. gender, good psychosocial functioning pre-transplant) and the selection of the measures (making comparison with other studies difficult). On the other hand, our results add to the growing evidence of psychological outcomes in facial transplantation.

Although most psychosocial functioning of both participants was pre-transplant within a normative and healthy, there was some discrepancy between the partner and the patient own sense of pre-transplant emotional health. The latter was more in line with the patient's other psychological measures. It may reflect the difficulty of the partner as an external observer to differentiate between the emotional and physical health of the patient 3 months post trauma or it is likely to be the result of differences in coping between both partners.

The findings of this study are in line with previous reports pointing to positive psychological outcomes after facial transplantation (12-15). However, some studies report rather an initial decrease of psychological functioning and quality of life immediately after the transplantation and only an improvement at follow-up (14, 15). Patients have often adjusted to their injury deficits pre-transplantation and the extensive rehabilitation and new functional limitations after transplant may lead to temporary decreases in quality of life. Since no comparison with other composite tissue transplant patients at our centre was possible (e.g. the patient is single transplant patient) it is not clear how the patient's time from injury to transplantation has influenced our results. However, our findings may partly be explained by the successful surgery and the quick and good recovery of the patient post-op, which may have instilled hope in the patient and the partner. It is also likely that the good pre-op psychosocial functioning of both participants may have added to these findings. During the first 13 months after surgery, the patient has suffered from many and severe medical complications mainly caused by the pharmacological treatment. It may have contributed to the decrease of most psychosocial measures at follow-up and definitely to the low score on physical quality of life. It may also explain the low perceived marital support and depth of the partner at follow-up since the patient was probably feeling too ill and too preoccupied with the medical problems and therefore paying less attention to the needs of his partner. Also, the frequent admissions to the hospital may partly explain this. The lower follow-up scores may also reflect the patient and the partner going back to their normal (pre-transplant) levels once the 'transplant honeymoon blues' was over. However, longer follow-up research is necessary (and currently planned up to 5 years after surgery) to further investigate this.

Surprisingly, most domains of psychosocial functioning of both patient and partner (including the mental quality of health of the patient) always remained within a healthy and normative range in spite of the severe medical complications. Contrarily, some measures such as competence, acceptation, affective responsiveness, communication, and disease benefits as reported by the patient, even improved. Different explanation may be possible. As previously mentioned, one may argue that the good psychosocial functioning and the personality characteristics of both partners before the transplant may have contributed to these findings (51 - 53). Further, several authors have already suggested that an accommodative coping style with acceptance of the illness more than illness characteristics, predict the mental quality of life of chronically ill patients (54, 55). The high palliative and avoidant coping of the patient may point rather to accommodative coping style than an assimilative coping style, which is often characterized by repeated unsuccessful attempts to solve the problems associated with a chronic illness. The high resilience of both partners pre-transplant may not only have helped them to overcome the difficulties associated with the transplant surgery and the medical complications but also to become stronger persons in a stronger relationship and family. It is difficult qualitatively to explain the nature of the resilience of both partners except that they often mentioned that 'there's no other option than to go through with it'. It is also likely that the intensive psychological and psychiatric support for both the patient and the partner may have supported the couple to better cope with these difficulties. Consequently, it may emphasize the importance of involving the caregivers in the psychological treatment since facial transplantation may affect the partner and the marital relationship (15, 56).

Finally, it is difficult to examine how the blindness of the patient may have played a role in the individual and family outcomes since the patient was blind from the start of the study. At baseline, the patient showed already good psychosocial functioning despite the relatively recently acquired blindness. The blindness did not affect the compliance with and the ability to participate in rehabilitation and the social re-integration of the patient in any way, although the patient has expressed during the psychiatric treatment that being blind was not always easy. One may argue that good psychosocial functioning and marital support pre- and post transplant may be of more importance to predict good outcome than the blindness itself, which in our opinion is irrelevant to facial transplantation (21). But, it may be possible that long-term social reintegration will be more affected by the blindness than by the facial transplantation. More research is necessary to further investigate this.

Conclusions

The preliminary findings of this study further support positive psychosocial outcomes after facial transplantation. Moreover, it is also in favor for the expansion of inclusion criteria of facial transplantation to blind patients. Finally this study may underscore the importance of good psychosocial functioning pre-transplant and an intensive psychological and psychiatric treatment involving the family members for improving outcome.

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	Baseline		Post-op		15 months follow-up		reference values
	IP	P	IP	P	IP	P	
SEH self	4	3	4	3	4	3	1 (poor) - 4 (very good)
SEH partner	3	1	4	3	3	3	
BDI-II	6	6	0	3	6	4	0-63, 0-13= minimal
State anxiety	30	27	20	22	26	29	34,3(8,3)M 35,2(8,4)F
Trait anxiety	31	24	20	22	28	27	36,1(8,4)M 37,7(8,4)F
Hopelessness	4	5	1	1	2	3	≥9 = suicide risk
Illness cognitions							
Helplessness	16		8*		16		6 (poor) - 24(very good)
Acceptance	17		24*		19		
Disease benefits	10		24*		18*		
Quality of life							
Physical health	60		95*		35.6*		0 (poor) - 100 (very good)
Mental health	96.7		98.7		95.6		
Total	78.4		96.9		65.6		
Coping							
Active problem solving	22	22	22	25	22	25	
Palliative reaction	14	20	15	21	20*	23	
Avoidance	12	17	13	21	18*	16	
Socialization	11	21	15	17	12	17	
Passive reaction	10	7	7	7	7	8	
Expression of emotions	3	3	3	5	4	4	
Reassuring thoughts	9	12	10	16	12	15	
Resilience							
Competence	58	63			68*	65	25 (poor) - 100 (very good)
Acceptation	29	31			32*	30	
Resilience total	87	94			100*	95	
Marital support							
Support	3.6	3.6	3.8	3.6	3.4	2.8*	3,35(0,46)M 3,31(048)F
Conflict	1.5	1.2	1	1.2	1.4	1.3	1,95(0,45)M 1,94(0,45)F
Depth	3.8	3.8	3.8	3.3	3.7	3.2*	3,41(0,46)M 3,41(0,47)F
Family functioning							cut-off, < =healthy functioning
Problem solving	1.7	1.7	1	1.5	1	1.3	2,2
Communication	1.9	2	1.3	1.8	1.1*	2	2,2
Roles	1.3	1.2	1.4	1.3	1.1	1.4	2,3
Affective responsiveness	2.8	1.7	1.2*	1	1.5*	1.5	2,2
Affective involvement	1.3	1.3	1.4	1.1	1.4	1.4	2,1
Behavior Control	1.2	1.2	1.3	1.4	1	1.2	1,9
Global Functioning	1.3	1.4	1.2	1.2	1.2	1.2	2,0
Dyadic adjustment							
Affectional expression	12	10	12	8	12	11	total < 100 = significant relationship distress
Consensus	65	52	65	58	65	60	
Satisfaction	44	44	47	40	40	41	
Cohesion	16	17	18	20	18	20	
Total	137	123	142	126	135	132	

IP=patient, P=partner, SEH=subjective emotional health, BDI-II=Beck depression inventory-II, M=male, F=female, *=RCI>1,96

Table 8.1:
Psychological and marital functioning of the facial transplant patient and partner, pre- and posttransplant and at 15 months follow-up.

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CHAPTER 9

Long-term multifunctional outcome and risks of facial vascularized composite allotransplantation

Based on:
Nathalie A Roche*, Phillip N Blondeel*, Hubert F Vermeersch, Patrick C Peeters, Gilbert MD Lemmens, Jan de Cubber, Miet De Letter, Kristiane M Van Lierde. Long-term multifunctional outcome and risks of face vascularized composite allotransplantation. *J Craniofac Surg 2015 (submitted).*
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Abstract:

Introduction: Vascularized Composite Allotransplantation (VCA) to reconstruct complex centrally located facial defects and to restore vital functions in a one-staged procedure has worldwide gained acceptance. Continuous long-term multidisciplinary follow up of face transplant patients is mandatory for surveillance of the complications associated with the immunosuppressive regime and for functional assessment of the graft.

Methods: In December 2011, our multidisciplinary team performed a digitally planned face transplant at the Ghent University Hospital, Belgium on a 55-year-old man with a large central facial defect after a high-energy ballistic injury. The patient was closely followed by the team to assess functional recovery, immunosuppressive complications, overall well-being and quality of life.

Results: Three years postoperatively, the patient and his family are very satisfied with the overall outcome and social reintegration in the community is successful. Motor and sensory functions have recovered near normal. Infectious and medical complications have been serious but successfully managed. Immunosuppressive maintenance therapy consists of corticoids, tacrolimus and mycophenolate mofetil in minimal doses. Epithetic reconstruction of both eyes gave a tremendous improvement on the overall aesthetic outcome.

Conclusion: Despite serious complications during the first 12 months, multifunctional outcome in the first face transplant in Belgium (#19 worldwide) is successful. This success should be attributed to the continuous and long-term multidisciplinary team approach. As only few reports of other face transplant patients on long-term follow-up are available, more data need to be collected to further outweigh the risk benefit ratio of this life changing surgery.

Key words:

Vascularized composite tissue allotransplantation; face transplantation; multifunctional outcome; multidisciplinary team

Introduction

The face plays a central role in identity, attractiveness and social interactions. Of all physical handicaps, none is more devastating than facial disfigurement. It severely affects social interactions and one's perception of self-image often leading to psychological problems including suicide, discrimination by others and exclusion from society and normal life (1 - 3).

Vascularized Composite Allotransplantation (VCA) of the face to restore aesthetic appearance, overall well-being and vital facial functions such as breathing, swallowing, mastication and other social functions such as speech and non-verbal communication in a single procedure was introduced in 2005 as an option for patients with complex, devastating and otherwise non-reconstructable deformities. (4). Since then 34 cases have been performed worldwide with overall favorable functional outcomes and a mortality rate of 13% (5). However, reports on functional outcome beyond 2 years have been rare and are inconsistently defined (6 - 14). Recent studies suggest effectiveness of facial VCA in both increasing quality of life as well as the potential to prevent life-threatening complications (14, 15). In order to optimize outcomes and minimize adverse effects associated with the immunosuppressive therapy in these patients, long term follow-up and reporting by the multidisciplinary team involved in the treatment is of paramount importance to provide further insight and define the best surgical and medical strategy for facial VCA.

Three years after the first Belgian face transplantation (#19 worldwide), we report the progress in aesthetic outcome, functional recovery of the allograft as well as the overall condition and quality of life of the patient. Additionally we report on the lessons learned from this case.

Methods

Transplantation

Face transplantation (FT) planned by computerized 3D modeling, was performed in a 55-year-old man with a central facial defect after a ballistic injury. Five days after the injury, the patient underwent a temporary reconstruction with a plicated free anterolateral thigh flap to close the defects and separate the oral and nasal cavities. One year later a VCA consisting of bilateral maxillae, hard palate, part of the left mandible and the soft tissues of the lower 2/3rd of the face was performed. The donor was a 22-year-old male with irreversible traumatic brain injury matching our patient in race, skin complexion and facial morphology. Details on the surgery, postoperative course, rehabilitation and early postoperative outcome have been previously described (16 - 20).

Additional surgical procedures

Twenty-six months after the face transplant, correction of the tracheostomy scar was performed under general anesthesia in combination with the placement of Brånemark implants in the superior orbital rim of the left eye socket. Three months later, a fitting epithesis was fabricated by our team's anaplastologist (JDC) to recreate the left upper eyelid and eye. Additionally, after some remodeling of the right eye socket, a classic eye prosthesis could be fitted on the right side. The color of the iris in the epithesis as well as in the classic eye prosthesis was chosen after carefully studying his pre-traumatic pictures. No further revision procedures have been performed.

Evaluation Procedure

Postoperatively the patient was seen on a monthly basis by the immunologist of the team. Evaluation by the surgeons and speech therapists involved was done on a 3 monthly base or more frequent if necessary. The members of the multidisciplinary team met on a regular basis to discuss the present outcomes and to formulate the best treatment strategy. Three years postoperatively, all involved team members individually evaluated and tested the patient and wrote a detailed medical report. Additionally, a comprehensive review of the patient's medical record was performed to define overall outcomes and complications.

Sensory function

To evaluate recovery of sensation in the allograft, stimulation with Semmes-Weinstein light touch monofilaments was performed and recorded according to Brezezicki and Siemionow (21, fig 9.1).

Speech

Speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior were assessed by two experienced speech language pathologist (KVL, MDL) aiming at a consensus score as described previously (17, 18).

Quality of life/psychological outcome

Psychological evaluation took place on a monthly basis. At 3 years post transplant, psychiatric assessment was performed using the Mini International Neuropsychiatric Interview (MINI, Dutch version 5.0.0, section A to O) (22). The Facial Disability Index questionnaire was administered to evaluate the patient's physical function and social/well-being function (23).

Results

Immunological aspects

The patient experienced one episode of acute graft rejection 4 months postoperatively, proven by facial skin and oral mucosa biopsies. Rejection was successfully treated with methylprednisolone intravenous (IV) and hyperimmune cytomegalovirus (CMV) immunoglobulins IV for 4 days. No other episodes of rejection have been encountered since then. As there were no further clinical signs of acute or chronic rejection, biopsies were not performed systematically. Immunosuppression was slowly tapered to methylprednisolone 4 mg daily, mycophenolate mofetil 500 mg bi-daily (BID) and tacrolimus 0,5 mg BID with targeted trough levels around 4 ng/ml; no rejection of the graft was noticed throughout this entire episode. We did not experience graft versus host disease.

Postoperative complications

Our patient suffered of a number of immunosuppressive drugs related side-effects during the first 12 months after the transplant. Complications are summarized in Table 9.1. The most severe complication was a pulmonary aspergilloma, which could be treated successfully by antifungal medication (16).

Thirty-one months post transplant he developed discrete myalgia, weight loss of 1 kg with dyspnea but without fever. While all previous 3-monthly follow-up radiologic examinations were stable, only demonstrating fibrous scarring of the old aspergilloma lesions, CT-scan showed a new lesion in the left upper lung lobe while galactomannan testing was positive. Treatment with liposomal amfotericine B Ambisome IV was interrupted after 48 days because of rising serum creatinine levels to 2,1 mg/dl; caspofungine 50 mg daily IV was continued for 24 days, since oral maintenance azole therapy had previously led to syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). Within the 48 days of Ambisome therapy, the patient already had full clinical recovery and a major radiological amelioration of the pulmonary lesion. Renal function returned to baseline after cessation of Ambisome. Follow-up evaluation at 37 months post transplant showed further radiological clearing of the old aspergilloma lesions in a patient with a good overall physical condition.

Aesthetic outcome of the allograft

After healing of the implants, the epithesis and eye prosthesis were placed resulting in a tremendous improvement of the overall visual and aesthetic outcome result of the allograft (Fig. 9.2 - 9.5). The patient and his partner report that outsiders who had not known him before his accident almost never notice that facial surgery was performed.

Sensory recovery of the allograft

Gradual improvement in sensation was noticed in time; the patient reports that he experienced tingling until 31 months postoperative and sensation continued to improve until then. No changes have occurred afterwards and tingling completely disappeared. Figures 9.6, 9.7 and 9.8 show the topographic evolution of the sensory recovery at 3 months, 8 months and 37 months postoperative respectively. At 37 months postoperative, sensation of the face has returned to normal in 85% of the graft. Only in the region of the left infra-orbital nerve, the left side of the nose and left lower lip anesthesia has remained. The patient reported normal taste and smell.

Speech

A summary of the results can be found in Table 9.2. Earlier results have been reported previously (17, 18).

Speech intelligibility and acceptability

Speech intelligibility (100% consensus evaluations of words, sentences and spontaneous speech (24, 25)) is normal on word and sentence level and in functional conversations. Speech acceptability (consensus evaluation 100%) (24) is judged as slightly impaired.

Voice and resonance

The Voice Handicap Index (25) showed no psychosocial impact of the vocal problem on the quality of life (score 10/120; reference <20/120= no disabilities). All the vocal characteristics are perceptually judged (consensus evaluation 100%) as normal. Moreover the objective vocal quality by means of the Dysphonia Severity Index (28) has a value of +3.2 reflecting a normal objective vocal quality. Three years post-transplantation a moderate hypernasality is still present (consensus evaluation 100%). The nasalance (27) values of the vowels and the sentences were increased in comparison with the normative data.

Articulation

The phonetic inventory was complete from 1 month postoperative until the last assessment. Four phonetic disorders of the bilabials (/p/, /b/, /m/, /w/) remained present.

Oromyofunctional assessment

During the last assessment all lip functions were present but still decreased and all tongue functions were normal. Swallowing and mastication were normal. The results of the Oral Health Impact Profile (30) showed no impact of the oral health on the quality of life.

Motor recovery

A discrete muscle contraction was electromyographically detectable one month postoperative, followed by a gradual increasing amplitude in the course of the following months (20). The first active and controlled smile was seen at 4 months. Six months post transplant, the patient could lift both oral commissures

independently and non-verbal communication and facial expressions were returning with nearly normal mouth closure as a result of improved tonicity of the soft tissues and disappearance of the initial swelling. Over time, the graft has continued to improve in appearance and function (Fig. 9.9 - 9.11).
At 37 months, non-verbal communication and facial expressions have recovered, however minimal asymmetry between both sides of the face persists with slight muscle weakness left. He is able to move each side of the face independently in the different sub-regions of the facial nerve without synkinesis or mass movements (Fig. 9.11 - 9.13).

Overall evaluation of wellbeing and quality of life

We reported earlier on the psychological, marital and familial outcomes at 15 months (19). Three years post transplant, the patient is psychologically and socially doing very well. He shows no symptoms of any psychiatric disorder (e.g. depression, post-traumatic stress disorder, psychotic disorder, anxiety disorder, alcohol or substance use disorder). He has not been taking any antidepressant or psychotropic medication during the last 2 1/3 years. Over the last year psychiatric follow-up was reduced to a monthly consultation. He experiences the transplant as self-evident and reports good marital and family functioning. His participation in family and social activities, which is not affected by the face transplant in any way, has reached similar levels as before the facial trauma. Contrary, FT has given the patient the possibility to re-integrate in the society without feeling stigmatized or experiencing negative social reactions. Strangers see him merely as a blind person as the face transplant is hardly noticed. This is in strong contrast with his life after the trauma and before the transplantation, when he never left the house. Although the patient has adapted well to the blindness, the nature of some social activities has changed and his daily life is restricted by it. The Facial Disability Index (both physical and social well-being functions) showed a minimal physical and psychosocial disability of the facial neuromuscular functioning (table 9.2).

Discussion

In this report, we present the 3-year multifunctional outcome of a patient who underwent a partial osteomyocutaneous face transplantation for severe facial disfigurement caused by a ballistic injury. A facial VCA was expected to restore vital functions and aesthetics in a one-stage procedure. Offering VCA a as primary choice avoids multiple conventional reconstructive attempts, spares the patient years of continued disfigurement, malfunctioning and pain both in face and donor areas and reduces the cumulative financial and psychological burden (7, 8, 12, 31 - 33).

As highlighted in other reports, many logistic and surgical questions of face transplantation have been resolved over the years, but the question of long-term consequences of immunosuppression remains a concern (8, 10, 12, 13). Infectious complications often occur and the most severe therapy related complication in our patient was a pulmonary aspergilloma, with a relapse 31 months post-transplant. We experienced no systemic side effects related to the immunosuppressive therapy. In general, the incidence of these complications is low in contrast to solid organ transplant patients as face transplant patients are in general good health (13). By multidisciplinary team approach, infectious and medical complications can be adequately diagnosed and treated. This is important for minimizing the impact on overall quality of life. Other CTA-groups have shown similar experience (8, 13 - 15, 34).

Face transplantation has an extraordinary restorative capacity in a single procedure but often involves different types of minor revision surgery (13). We performed epithetic reconstruction of the left eye socket to increase the overall aesthetic outcome of the graft and to our knowledge this has not yet been described. Anaplastology led to a tremendous improvement of the overall aesthetic outcome. We consider it as a very useful adjunctive tool in FT for reconstitution of difficult to reconstruct structures such as ears and eyes.

Sensory recovery started 5 months postoperatively; at 37 months, sensation of the face has returned to normal to slightly diminished on the right side. Smell and taste were normal, while strongly impaired before FT. On the left side impaired sensation was observed, with persistent anesthesia in the region of the infraorbital nerve and left lower lip. Face transplantation is only useful in facial reconstruction if all functional components (sensory function, motor function, resurfacing) of the face as a unit can be reconstituted. Without sensation optimal facial functioning is not possible. Therefore it is critical to perform sensory repair, in order to optimize nerve regeneration. Although spontaneous sensory recovery has been reported without nerve repair, it did not occur in our patient and the results show that recovery is better when nerve repair has been performed (13, 14, 33, 37). Sensory recovery after FT precedes motor recovery. The sensory input is crucial during rehabilitation as the cutaneous receptors in the face play an important role providing proprioceptive information on facial movement. As the allograft becomes more innervated (motor and sensory), it evolves into a functioning organ reacting with the outside world. Consequently, representation, reorganization and reintegration in the motor and sensory cortices become more complete (37).

Motor function has returned to near normal, with a slight facial asymmetry between the right and left side. Separate repair of all facial nerve branches was performed; despite this, the left side has remained slightly weaker and has less muscle excursion. We feel this has probably to do with the extensive scarring and tissue and nerve damage at the left side caused by the initial trauma.

An early, intensive rehabilitation program helps to improve allograft function and is critical for the recovery of the facial musculature (8, 13, 38). The findings of this study show that the overall speech intelligibility is normal, also during the spontaneous speech. In other reports patients were able to speak and to produce intelligible speech, however few detailed data of the speech analysis are provided in these studies (33, 34, 36). Speech acceptability in this patient is still slightly impaired 3 years after transplantation. The vocal characteristics and the tongue functions are normal but the lip functions are decreased. The articulation of 4 bilabials is still difficult and probably caused by a combination of motor dysfunction and a lack of sensation in a large area (60%) of the lips. Also the presence of the moderate hypernasality might need further intervention.

The good psychosocial outcome of the patient may be explained by the strong family support during and after the transplantation, his premorbid good psychosocial functioning and optimistic attitude. This underscores the importance of critical patient selection for this procedure. Despite the serious medical complications that posed a severe burden not only to the patient but also to his family, they reported that the final result was worth it. When specifically asked if they would repeat the procedure if they had known everything beforehand, they promptly confirmed to do so and mentioned they quickly had forgotten about the negative aspects. For them, the transplantation has given hope, a new future and the ability to resume their lives, which he and his family would not have done if he were still facial disfigured.

The results also give further support to include well-selected and motivated blind patients in protocols for face transplantation (39). We feel they have even more psychological benefits of the knowledge of having a normal facial appearance; our patient mentioned that people see him as a blind person and not as someone with a facial disfigurement since they do not notice the allograft. The patient has well integrated the face transplant into his existing body image and sense of identity and refers to it as "my face".

Our overall findings are in accordance with other reports and hopefully will contribute to further support and optimize face transplantation and outcomes. The major limitations of this report are that the conclusions are based on a single patient experience. It remains difficult to compare our results with other cases as during the last 9,5 years, 34 cases have been performed in 10 different centers, few long-term follow-up reports with results from objective assessment techniques and consensus evaluation exist and each case is unique. Another limitation is that we did not perform subjective and objective assessments on aesthetic outcome, as one of the goals of facial VCA is to restore aesthetics. Aesthetic quality parameters can be obtained using the validated Patient and Observer Scar Assessment Scale (40). Subjective and objective assessment by the patient is difficult due to his blindness. However the family and non-informed individual observers could have been assessed pre- and postoperatively and this is a topic for future research.

Conclusion

Based on our outcomes, we conclude that the risk-benefit ratio of face transplantation in this specific case is positive and that the transplantation has been life changing psychologically. Multidisciplinary team approach, intensive rehabilitation program and prompt and adequate treatment of complications have proven to be essential. Additionally, anaplastology resulted in a tremendous aesthetic improvement of the graft. More systemic long-term data need to be collected and reported by other face transplant centers in the future to further decide whether the physical and psychological outcomes are worth the risks and complications associated with the life-long immunosuppression needed for a surgical procedure that is life changing and offers new hope to severely facial disfigured patients.

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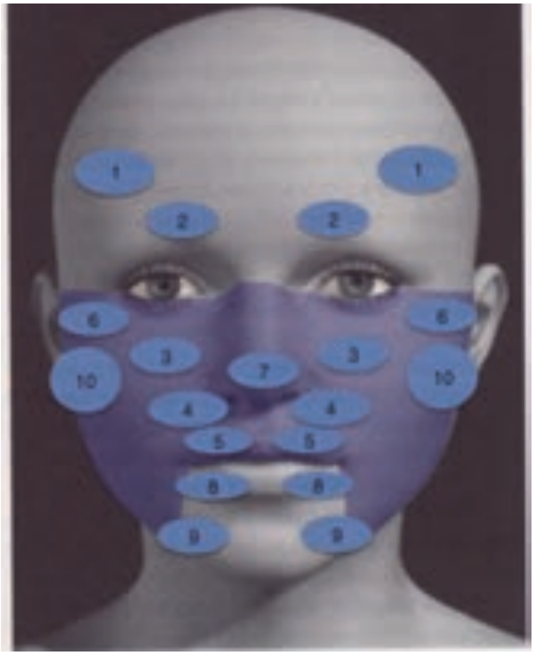
Ethical approval was obtained by the Ethics Committee of the University Hospital of Gent in accordance with the principles of the Declaration of Helsinki (file nr. 2001/022).



Trigeminal nerve (V):

V1: 1. - lateral forehead (3 cm lateral to the midpupillary line and 3 cm above eyebrows line - *supraorbital nerve*

2. - medial forehead (midpupillary line, 1 cm above eyebrows line) - *supraorbital nerve*

V2: 3. - maxilla (midpupillary line, 3 cm below the center of the pupil) - *infraorbial nerve*

4. - nasolabial fold (in the middle of the fold) - *infraorbital nerve*

5. - upper lip (1,5 cm lateral from the midline, 0,5 cm above the upper vermillion border- *infraorbital nerve*

6. - zygoma (3,5 cm lateral to the midpupillary line, 2 cm below the center of the pupil) - *zygomaticofacial nerve*

7. - tip of the nose - *external nasal nerve*

V3: 8. - lower lip (1,5 cm lateral from the midline, 0,5 cm from the lower vermillion border) - *mental nerve*

9. - mentum (medial epicanthal line, 2 cm below lower vermillion border) - *mental nerve*

Greater auricular nerve:

10. - preauricular area (2 cm below the tip of the tragus, 2,5 cm medial to the tragus) - *anterior branch of great auricular nerve*

Fig. 9.1:

Face allograft areas (according to Brzezicki and Siemionow).

Time point	**Event**	**Management**
Day 13	1 positive *Aspergillus fumigatus* sputum culture, asymptomatic	itraconazole 100 mg oral
Day 21	eyesockets and sinus colonisation *Pseudomonas Aeruginosa*	cotrimoxazole 400/80 mg BID oral
Month 1	impaired glucose tolerance testing	metformin 500 mg BID oral
Month 3	abscess osteosynthesis screw mandibula	drainage abscess/ removal screw; switch itroconazole to voriconazole 200 mg BID oral
Month 3	SIADH hyponatriemia 124 mmol/L (after 8 days voriconazole)	switch voriconazole to caspofungin 50 mg IV maintenance
Week 15	Grade IV graft rejection; sinusitis *Pseudomonas Aeruginosa*	methylprednisolone 500 mg IV for 4 days; hyperimmune CMV IVIG 2g/kg for 4 days; ciprofloxacine 500 mg BID oral
Month 5	pulmonary *Aspergilloma* lesions on CT scan	switch caspofungin to posoconazole 400 mg BID oral
Month 5	SIADH hyponatriemia 128 mmol/L (after 16 days of posoconazole)	stop posoconazole, restart voriconazole 200 mg BID oral
Month 6	asymptomatic CMV viremia with UL-97 mutation resistant to valganciclovir	reduction of immunosuppression hyperimmune CMV IVIG
Month 7	relapse SIADH	stop voriconazole; CT scan no *Aspergilloma* lesions
Month 7	painful osteoporotic thoracic vertebral fractures	diphosphonate zoledronic acid; fentanyl patches, analgesia, orthopaedic corset
Month 8	2 days of stupor related to hyponatriemia 116mmol/L combination of citalopram/fentanyl patches and immunosuppressive drugs	stop citalopram and fentanyl patches
Month 11	relapse pulmonary *Aspergilloma*	amphotericin B lipid complex IV 5 mg/kg
Month 11	nefrotoxicity after 3 weeks of Abelcet IV	switch to liposomal amphotericin B IV 3 mg/kg for 2 weeks
Month 11	pneumonia *Pseudomonas Aeruginosa*	tazobactam 4 x 4 gr IV
Month 31	relapse pulmonary *Aspergilloma*	liposomal amphotericin B IV 3 mg/kg for 48 days
Month 32	serum creatinine 2,1 mg/dl	switch ampho B to caspofungin 50 mg IV during 24 days

Table 9.1:
Overview of complications after face transplantation.
BID = bidaily, IV = intravenous, CMV = Cytomegalovirus, IVIG = intravenous immunoglobulins.

Post-operative results	3 years post-op	Reference
Speech intelligibility		
Consensus perc. evaluation		
Words	0	0(De Bodt, Guns & Van Nuffelen, 2006)
Sentences	0	0
Spontaneous speech	0	0
Dutch speech intelligibility score		
Words (%)	86	100(Van Den Steen et al., 2006)
Sentences (%)	95	100
Speech handicap Index	20	5/range: 4-6
Speech acceptability	1	0 (Dagenais, Brown & Moore, 2006)
Voice		(Jacobson & Johnson, 1997)
Voice Handicap Index	10	<20/120 no disabilities
Consensus perceptual evaluation		(Hirano, 1981)
Vocal quality	G0R0B0S0	G0R0B0A0S0
Pitch	0	0
Intensity	0	0
		(Baken & Orlikoff,2000)
Aerodynamic measurement		
Maximum Phonation Time (seconds)	25	22/range:6.7-37
Vocal range		
Softest intensity (dB)	60	51 (range:46-57)
Loudest intensity (dB)	99	97 (range:81-112)
Lowest frequency (Hz)	78	142 (range:96-188)
Highest frequency (Hz)	676	867 (range:453-1282)
Acoustic analysis		
Fundamental frequency (Hz)	97	122 (range:78-166)
Jitter	0.5	0.81(range:0-2.1)
Dysphonia Severity Index	+3.2	+2.5 (range -5 -+5) (Wuyts et al., 2000)

Table 9.2: Results (and reference data as found in the literature) of the assessments of speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior 3 years after face transplantation. The reference data (last column) are mentioned as criteria to evaluate the results.

Resonance		
Consensus perceptual evaluation		(Van Lierde et al., 2001)
Hypernasality	2	0
Nasal emission	0	0
Bzoch hypernasality test	10/10	0/10
Bzoch nasal emission test	0/10	0/10
Nasalance values		
Vowel /a/ (%)	31	20(range: 0-49)
Vowel /i/ (%)	44	26(range: 0-55)
Vowel /u/ (%)	37	9 (range: 0-24)
Oronasal passage (%)	50	34 (range: 23-45)
Oral passage (%)	46	11(range: 2.5-20)
Articulation		
Consensus perceptual evaluation		
Phonetic inventory	22/22	22/22
Phonetic analysis (amount and specific consonants distorted)	4 /pbmw/	0
Oromyofunctional behaviour		
Consensus perceptual evaluation		
Lip function		
Lip position at rest	1	0
Lip closure	1	0
Dispersion of the corners of the mouth	1	0
Lip protrusion	1	0
Lip strength	1	0
Lip position during swallowing	1	0
Tongue function	0	0
Tongue position at rest	0	0
Tongue protrusion	0	0
Tongue retraction	0	0
Tongue lifting	0	0
Tongue depression	0	0
Lateral tongue movements	0	0
Blowing	absent	
Oral Health Impact Profile		
Total score	8/56	0/56
Facial Disability Index		
Physical function (%)	75	100
Social/well-being function (%)	76	100

Figure 9.2:
Frontal view of the patient at 37 months post transplant as he appears in daily life wearing glasses.

Figure 9.3:

Left lateral view of the patient wearing glasses.

Figure 9.4:

Close-up picture of eye sockets before epithetic and prosthetic reconstruction.

Figure 9.5:

Close-up picture of eye sockets after epithetic and prosthetic rehabilitation, note little details of vascular structures that have been included in the socket epithesis.

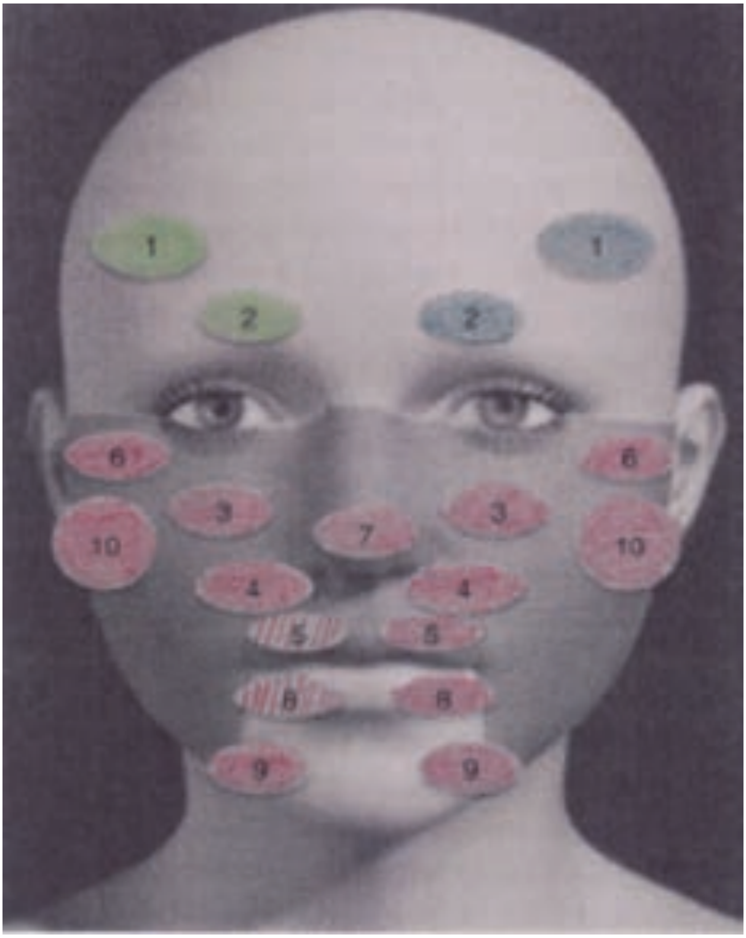


Figure 9.6:

Static Semmes Weinstein light touch monofilament test at 3 months postoperative; between brackets the amount of force in grams needed to bend a filament.

Green 2.36 - 2.83 (0,023 - 0,067gr)*:	normal sensation
Blue 3.22 - 3.61 (0,166 - 0,408 gr)*:	diminished light touch
Purple 3.84 - 4.31 (0,697 - 2,1 gr)*:	diminished protective sensation
Shaded red:	very impaired sensation
Red 4.56 - 6.65 (3,6 - 447,0 gr)*:	loss of protective sensation

*Birke JA, Brandsma JW, Schreuders TAR, Piefer A. Sensory testing with monofilaments in hansen's disease and normal control subjects. Int J Lepr 200;68(3):291-8.

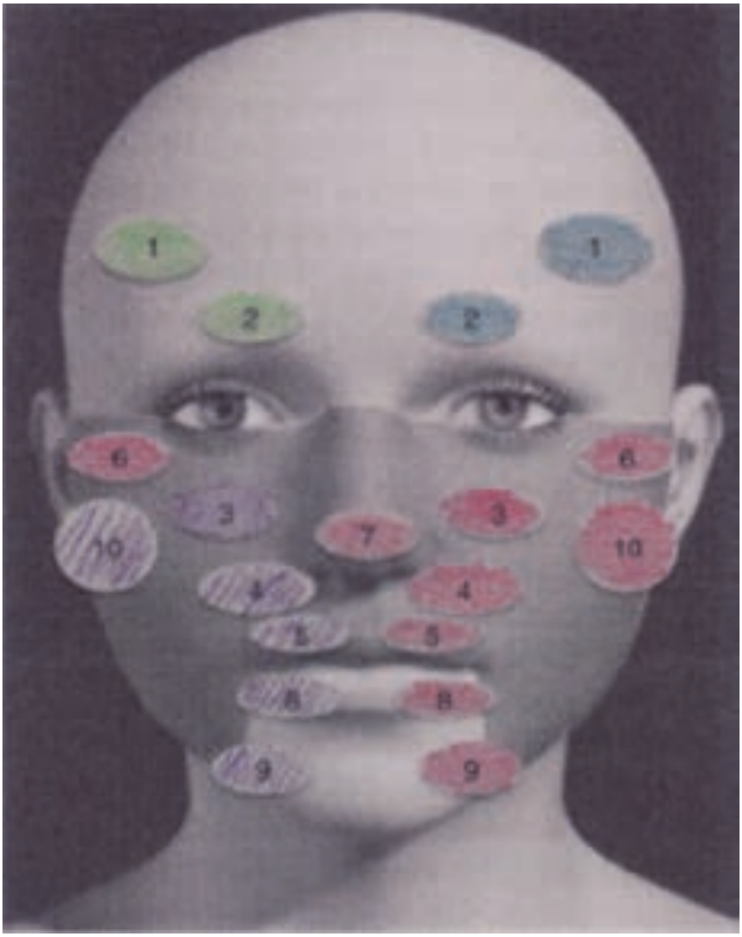


Figure 9.7:

Static Semmes Weinstein light touch monofilament test at 8 months postoperative; between brackets the amount of force in grams needed to bend a filament.

Green 2.36 - 2.83 (0,023 - 0,067gr)*:	normal sensation
Blue 3.22 - 3.61 (0,166 - 0,408 gr)*:	diminished light touch
Purple 3.84 - 4.31 (0,697 - 2,1 gr)*:	diminished protective sensation
Shaded purple:	very impaired sensation
Red 4.56 - 6.65 (3,6 - 447,0 gr)*:	loss of protective sensation

*Birke JA, Brandsma JW, Schreuders TAR, Piefer A. Sensory testing with monofilaments in hansen's disease and normal control subjects. Int J Lepr 200;68(3):291-8.

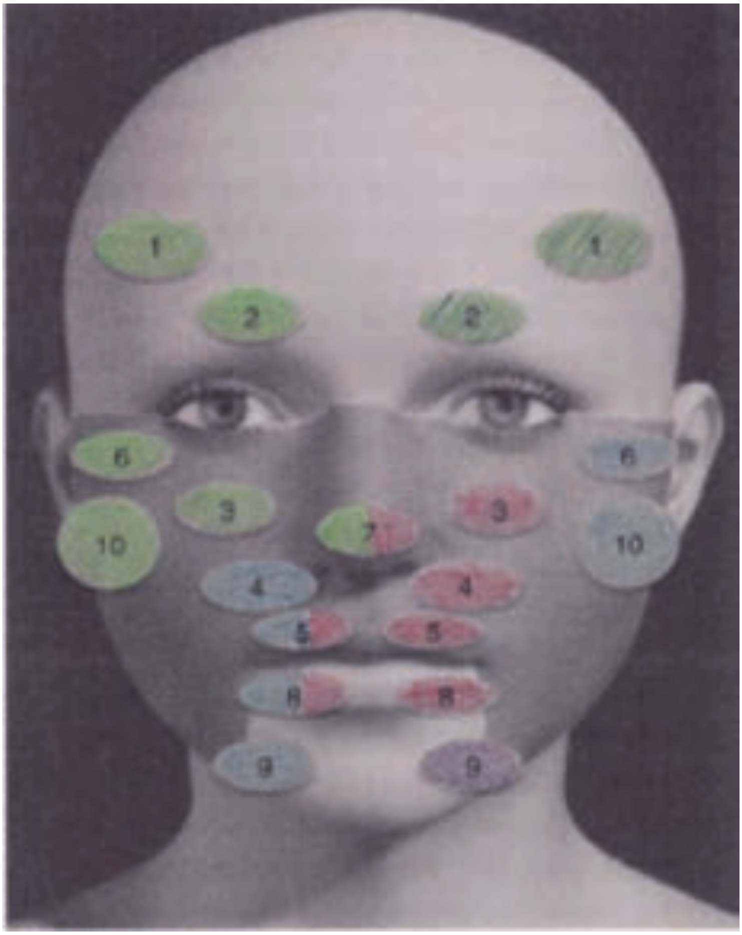


Figure 9.8:

Static Semmes Weinstein light touch monofilament test at 37 months postoperative; between brackets the amount of force in grams needed to bend a filament.

Green 2.36 - 2.83 (0,023 - 0,067gr)*:	normal sensation
Blue 3.22 - 3.61 (0,166 - 0,408 gr)*:	diminished light touch
Purple 3.84 - 4.31 (0,697 - 2,1 gr)*:	diminished protective sensation
toRed 4.56 - 6.65 (3,6 - 447,0 gr)*:	loss of protective sensation

*Birke JA, Brandsma JW, Schreuders TAR, Piefer A. Sensory testing with monofilaments in hansen's disease and normal control subjects. Int J Lepr 200;68(3):291-8.

Figure 9.9:

Frontal view of patient 6 weeks post transplantation, note general facial atonia and flaccidity.

Figure 9.10:

Frontal view at 16 months post transplantation.

Figure 9.11:

Frontal view with neutral expression at 37 months post transplantation.

Figure 9.12:

Frontal view with patient smiling at 37 months post transplantation.

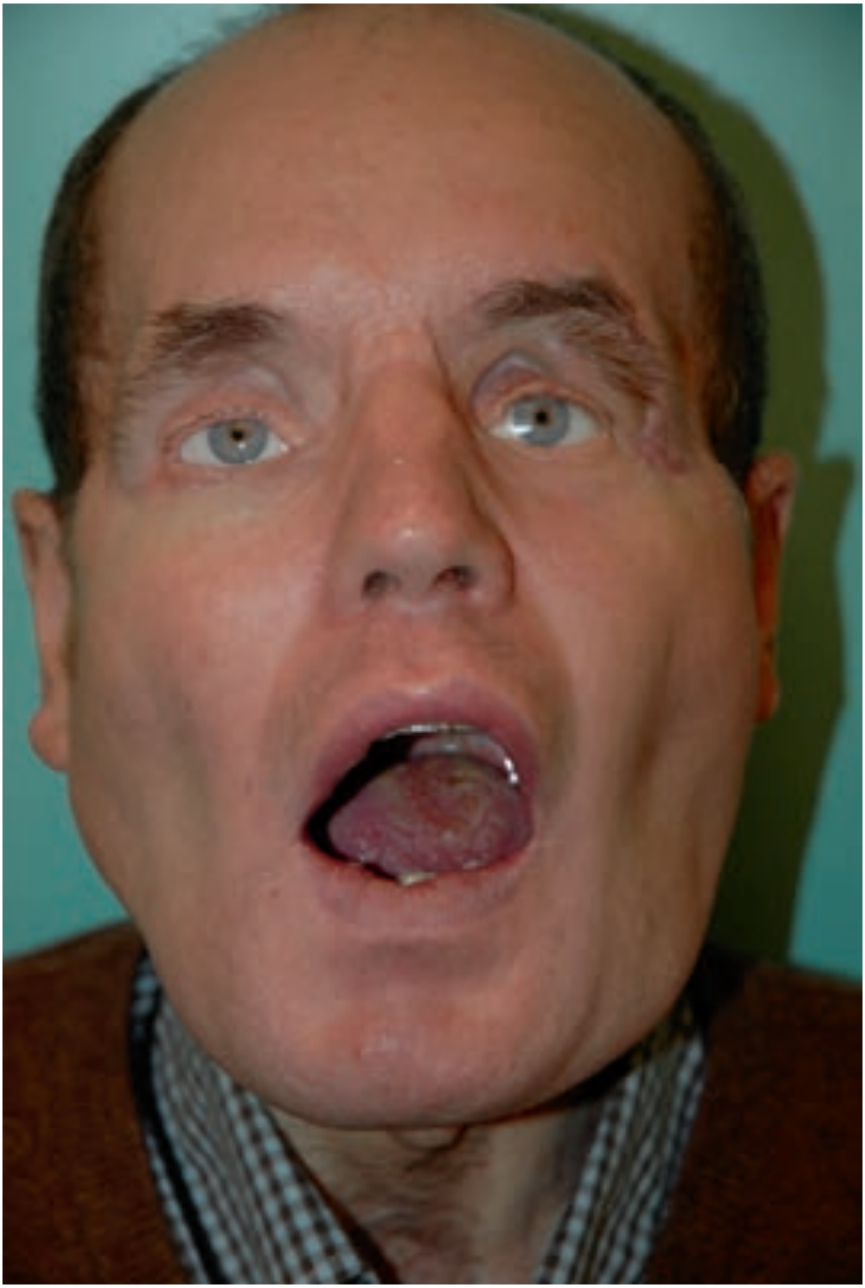


Figure 9.13:

Frontal view with patient opening his mouth at 37 months post transplantation.

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The essential difference between emotion and reason is

that emotion leads to action while reason leads to conclusion.

Donald B. Calne

Part 3

General Discussion and Summary

CHAPTER 10

General discussion and conclusions

In the past, surgeons often have been frustrated by the suboptimal functional and aesthetic results in facial reconstruction of centrally located defects where highly specialized tissues such as lips, nose and eyelids are nearly impossible to reconstruct with conventional plastic surgical techniques. This part of the face is unique and assures vital functions including breathing, mastication, swallowing and other social functions including speech and non-verbal communication. Of all handicaps, none has more impact on social, professional and psychological level as an extensive facial deformity (1, 2). Therefore the face should be considered as a vital organ that is essential in daily life (3, 4).
Facial transplantation (FT) was introduced in humans in 2005 as a possibility to reconstruct specialized tissues applying the principle of replacing "like with like" in a single procedure (5). Since the first face transplant, many technical, logistical and social aspects have been resolved. The outcomes of the first transplants have surpassed the initial expectations. FT has become a clinical reality and a new technique in the armamentarium of plastic and reconstructive surgeons. Probably one of the most important and critical parts of the process is choosing the right recipient. The potential recipient should be assessed by every member of the multidisciplinary team to decide whether face transplantation is the procedure of choice for the specific type of facial defect, considering well the risk-benefit ratio. Previous reports on the results in FT have shown that the key to success in this procedure lies in the selection of the appropriate patient who is stable, well motivated, therapy compliant and has amotivated environment. Besides the standard immunological matching criteria, an appropriate donor, matching the recipient in race, sex, skin type, length and height is of equal importance (6, 7).
After a preparatory phase of almost 3 years, we performed the first Belgian face transplantation in December 2011 in a 55-year-old man with a complex central facial defect after a high-energy ballistic injury. Considering the increasing positive world-wide experience in the value of this procedure as additional tool in reconstructive surgery, the general purposes of the current doctoral thesis were to assess all multidisciplinary aspects involved in FT of this specific case and to provide evidence that the benefits justify and even outweigh the

potentially associated risks. In the following paragraphs, the hypotheses of this thesis (chapter 3) will be discussed in detail.

In well-selected cases of patients with large central facial defects, facial transplantation offers the only possibility to restore anatomy, aesthetics, vital and social functions in a single procedure as it replaces "like with like" which is impossible with conventional surgical techniques.

Our patient suffered from a centrally located defect in the face, including almost all of the muscles of the mouth, a major part of the nose and left cheek. Previous reports have demonstrated that in selected cases, especially if the orbicularis oculi and oris muscle functions are lost, it is extremely difficult, if not impossible, to obtain good functional and aesthetic results with traditional plastic surgical reconstructive techniques (8 - 10). Even after multiple extensive reconstructive attempts, results are mostly very mediocre and pose an extra burden of continued disfigurement and pain in the face and donor areas of the patient (11, 12). In our patient, only one temporary reconstruction was performed in the acute phase to close the external defect and to separate the oral from the nasal cavity. We offered FT as an early option and single procedure to the patient and his family to perform an all-in-one reconstruction. The aesthetic outcome (chapter 4 and 9) and functional outcomes (subjective and objective assessment studies, chapters 5, 6 and 7) clearly demonstrate a result that would never have been obtained with conventional plastic surgery.

Three dimensional modeling and digital planning are valuable tools in planning facial composite tissue allografting (CTA) to improve accuracy and speed of the procedure.

In osteomyocutaneous face transplantations performed prior to our case, no specific techniques have been used to provide accurate 3D-planning of the surgery by obtaining precise measurements of the graft and fitting in the recipient. Nonetheless, these topics are essential for obtaining good aesthetic and functional outcomes. Three dimensional modeling and digital planning have already been used successfully in craniofacial, orthopaedic and cardiac surgery (13 - 15). We implemented this concept in our patient based on our experiences in facial surgery and anaplastology. The 3D-imaging and digital planning have proven to be valuable tools to save operating time, to determine the exact amount of bone needed in the upper and lower jaw and to obtain a good aesthetic result with a nearly perfect bony alignment. Additionally these techniques dramatically simplified this complex microsurgical procedure of extensive osteomyocutaneous allografting (chapter 4).

Meticulous pre-operative planning and continuous, long-term follow-up by a large multidisciplinary team are essential to build a facial CTA program.
Worldwide 34 reported cases of FT have been performed until now. When reviewing the available data of these patients, one can conclude that each case is unique and that no standard FT operation exists (chapter 1). After the operative indication has been set for FT and the patient is considered an appropriate candidate, it is mandatory to prepare and plan each case individually, to define the exact needs of the allograft and devise a plan for salvage in case of facial allograft failure.

A well-led and organized multidisciplinary team is another requirement for a successful program (chapters 2, 4 and 9). Other facial CTA centers already reported similar experiences (16 - 19).

We have shown that mock cadaver-training sessions with the complete surgical team, 3D modeling and digital planning are crucial for a smooth course of the entire surgical procedure (chapter 2 and 4). In an experienced microsurgical center, the chances of acute failure due to technical reasons are extremely low. In case of graft failure, which will most likely occur due to medical complications, a free flap for coverage of the face was still possible in our patient, since his potential donor-sites were not depleted as seen in cases of multiple previous salvage and reconstructive attempts.

During the first year after the transplantation, the patient suffered from several medical complications, including one acute rejection period. These issues had a serious impact in overall well-being and quality of life, not only for the patient but also his family (chapter 4, 6 - 8). Facial transplantation is a complex medical specialty involving so many aspects, such as surgery, immunology, infectiology, rehabilitation, etc. Only close monitoring and continuous evaluation of the multidisciplinary team allowed these problems to be handled and dealt with adequately, the same as in any other multidisciplinary medical specialty such as treatment of cleft lip and palate, congenital craniofacial malformations, head and neck oncology etc.

Anaplastology is indispensable when performing facial transplantation for reconstitution of the donor and as adjunctive tool for reconstitution of difficult to reconstruct facial structures in the recipient.

Restoration of the donor face is an essential requirement to preserve and respect the dignity of the donor and his/her family. Most other CTA centers handle the same requirement. This step is also essential to ensure cooperation of families and organ procurement agencies for future FT (20). Resin and silicon masks have been used with superior results obtained in the latter (16, 17, 21). Some centers exclude donors whose families desire an open-casket funeral. They claim that the donor's facial defect, even when restored with a mask, is not suitable for viewing (22).

We showed that high level anaplastology allowed the family to greet the deceased in a respectful and serene atmosphere without issues of unacceptable appearance of the donor's face (chapters 2 and 4). As the Ethics Committee did not allow contact between the surgical team and the donor family, feedback from the transplant coordinator was asked for evaluation. He reported that they were very satisfied about the way the donor and the family were (and still are) approached and counseled by the psychologists, treating physicians and transplant coordinator; recently the family participated in an assessment performed by the psychiatrist and psychologist of our team to evaluate their experiences. At the moment the results are under analysis and will be published in the future.

The severely disfigured face of our patient was reconstructed with FT. However, even with this procedure, some structures remain impossible or very difficult to reconstruct such as eyes and ears. Anaplastology for both eyes and left upper eyelid in our patient resulted in a tremendous aesthetic improvement of the graft and should be considered as very useful adjunctive tool. The patient and his partner report that outsiders who had not known him before his accident almost never notice that facial surgery was performed (chapter 9).

From a psychological point of view, facial transplantation is a life changing procedure, as it improves quality of life and overall well-being of severely facial disfigured patients.

Studies have shown that patients with an extensive facial deformity may suffer important psychological and social difficulties. Depression, anxiety, low self-esteem and quality of life, poor marital and social relationships and changes in body image have frequently been reported. An intact face is essential for non-verbal communication, speech and professional success (23-25).

After the trauma and before his face transplantation our patient was socially isolated and almost never left the house. Afterwards he experienced an overall improvement in quality of life and well-being (chapter 6 and 8). Due to the surgery the patient was able to re-integrate into the society without feeling stigmatized or experiencing negative social reactions. Additionally, the patient and his family reported that the transplantation has given them hope, a new future and the ability to resume their lives. They have confirmed that this would not have been possible if he was still facially disfigured (chapter 8 and 9).

The keys to success in facial transplantation lie in the selection of the appropriate patient who is stable, well motivated and therapy compliant and definition of the appropriate indication for this procedure. Blindness is not a contra-indication for face transplantation.

The topics of choosing the appropriate patient and blindness as contra-indication in FT were addressed in earlier reports (26 - 28). Patients also have to be motivated to follow the strict postoperative regimen of immunosuppressive therapy and intensive rehabilitation, as this is considered predictive of good outcome.

The excellent aesthetic outcome (chapter 4 and 9), the longitudinal progress in speech characteristics and oromyofunctional behavior (chapter 5 - 7) and the positive psychosocial outcomes (chapter 8) in our patient strongly add to the growing evidence of successful outcomes of FT. Additionally, the fact that the patient and his partner were willing to undergo all the extensive subjective and objective assessments (for evaluation of speech and motor/sensory recovery), psychological tests and psychiatric/psychological treatment pre- and postoperatively provides evidence for a stable, well-motivated and therapy compliant patient and family.

The blindness did not affect the compliance with and the ability to participate in rehabilitation and the social re-integration of the patient in any way. An adequate social setting, additionally to good psychosocial functioning and marital support pre- and posttransplant may be of more importance to predict good outcome than the blindness itself, which we consider as irrelevant to FT (chapter 8). Blind patients might even have more psychological benefits of the knowledge of having a normal facial appearance. In our patient, the allograft is hardly noticed by strangers as people merely see him as a blind person. All these results prove that our applied selection procedure was correct and led to the good overall 3-year outcome in our patient (chapter 9).

Strengths and limitations

This doctoral thesis has several strengths and limitations, which are summarized in table 10.1. Strengths include the relatively long and well-documented follow-up of 3 years and the detailed subjective and objective assessments on motor/sensory recovery, speech, oromyofunctional behavior (chapters 5 - 7, 9) and psychological outcomes (chapter 8). In the peer-reviewed literature, only few long-term follow-up reports on face transplantation are available. Reports with detailed assessments are even scarcer (9, 29 - 33). Additionally we identified the specific aspects in this FT case that led to success, such as digital planning and 3D-modeling, well prepared surgery, anaplastology etc., all discussed in the previous paragraphs.

We adapted and modified our strategy in FT based on issues we encountered in our patient.

1. Pre-operative assessments for speech and oromyofunctional behavior were not performed. To better define the impact of FT on overall speech intelligibility, it will be included in future cases.

2. Subjective and objective assessments on aesthetic outcome were not performed but will be included in the protocol.
3. The surgical approach has been modified including maximal sensory nerve repair (chapters 4 and 9) and better dealing with size mismatch between donor and recipient bone (chapter 4). In all future osteomyocutaneous face transplantations, 3D modeling and digital planning will be performed.
4. We also learned a lot from the acute rejection, the complications and medical problems the patient encountered (chapters 4, 8 and 9). In the future, we will be better able to anticipate on and approach these issues.
5. Despite the fact that the protocol well defined the aspects of dealing with the media, it turned out that this was not obvious and sometimes very hard and difficult to deal with. Stricter measures will be applied in future cases.

The major limitation of this doctoral thesis is that the findings and conclusions are based on a single patient experience. During the last 9,5 years, 34 cases have been performed in 10 different centers. All these cases are unique and exceptional. Surgeons and their surgical approach vary, objective assessment techniques and consensus evaluation techniques, if applied at all, are different and therefore it remains difficult to compare our results with other reported cases.

Another limitation is the lack of subjective and objective assessments on aesthetic outcome as one of the purposes of FT is to restore aesthetics. Aesthetic quality parameters can be obtained using the validated Patient and Observer Scar Assessment Scale (34). Subjective and objective assessment by the patient is difficult due to his blindness. However the family and non-informed individual observers could have been assessed pre- and postoperatively and this is a topic for future research.

Future perspectives

As absolute numbers for face transplantation are low, **the long-term goals of an established CTA center should include intensive collaboration between departments of the leading hospital and good communication between the different CTA centers in Europe within the setting of Eurotransplant** to establish centralized and highly specialized evidence based care for FT patients.

In this way, more feasibility and functional outcome studies can be performed to optimize outcomes of face transplantation.

We established a center that includes a program to treat disfigured patients who will benefit of CTA. Based on the experiences, described in this thesis, we were able to refine and ameliorate our protocol. In this way we will be able to perform more face transplantations in the future. On the long term the program will be extended to other types of CTA (such as hand, uterus) in collaboration with other departments of the hospital.

As many surgical problems around FT were solved, the main focus now lies on dealing with rejection, complications, optimal suppressive therapy and reporting on long-term functional outcomes. This will further outline the risk-benefit of this procedure. For these goals, the situation where all FT centers worldwide rapport their findings to the International Registry of Hand and Composite Tissue allotransplantation would yield an incredible amount of valuable information. It would make it possible to compare results and define the optimal protocol/regimen based on outcome. Unfortunately of all 34 FT performed world wide over the last 9,5 years, reports only exist on about 20 patients.

Hopefully, more advances in immunosuppressive therapy will be made in the future since the main drawbacks of face transplantation are not associated with the allograft itself but with the need for life long immunosuppressive therapy and its long-term side effects (opportunistic infections, secondary malignancies and cardiovascular morbidity) and potential mortality. In solid organ transplantation some advances have been reported in order to minimize chronic immunosuppression. Current protocols have relied on transient or sustained chimerism. This approach demands an intense preparation of the recipient before transplantation requiring a living donor and is not possible in CTA (35-37). If transplantation ever becomes possible without immunosuppression and the goal of donor-specific tolerance is achieved with preserved immunocompetence, CTA will certainly benefit and become more acceptable, not only for the face but also for other complex organs as feet, legs, genitals, etc.

Besides immunosuppression-related issues, the clinical practice of CTA is also limited by donor shortage. Tissue engineering (TE) is the generating of customized tissues in a laboratory setting using cells, biomaterials and bioreactors. Tissue engineering will eventually supersede CTA in clinic, because it bypasses donor shortage and immune suppression challenges. Many financial resources already have been invested in TE research and development, which are expected to result in a myriad of clinical products within the mid- to long-term. First, tissue engineers must address challenges such as vascularization of engineered tissues, oncological threats and maintenance of phenotype in culture. If these obstacles can be overcome, one can only hope that the lessons learned through decades of research in both CTA and TE will act synergistically to generate off-the-shelf composite tissues that can thrive after implantation in the absence of immunosuppression (38).

Conclusion

The purposes of this doctoral thesis were to describe and define the role of all the multidisciplinary aspects that are involved in FT and to provide evidence that success in facial transplantation depends on a well-led multidisciplinary team and appropriate screening and selection of the candidate by this team. As with any other complex medical problem, the only way to build experience and collect objective evidence to justify a procedure that is life changing and potentially associated with many medical complications is the establishment of centralized and specialized centers concentrating all necessary expertise. In this setting, FT will become an accepted procedure that gives hope and a new future to severely facial disfigured patients. FT centers should all have the responsibility to publish their outcomes in a transparent manner. Only then rigorous and strict guidelines can be elaborated on real indications for FT, which is an excellent reconstructive option in severely, but certainly not all facial disfigured patients. Additionally by providing objective and professional information, these patients should be made aware of the full and realistic indications and consequences of FT and that this procedure is not a panacea for every facial disfigurement.

The findings and results in the current thesis are in accordance with reports of other facial CTA centers and hopefully will contribute to support and optimize FT and outcomes in the future.

Strengths	Limitations
- Relatively long and well documented follow-up - Detailed assessments on speech and oromyofunctional behavior - Objective assessments on motor/sensory recovery - Detailed assessments on psychiatric and psychological outcomes of patient and partner - Identification of specific aspects in FT leading to success - Adaptation of FT protocol for treatment of future patients based on lessons learned from 1st Belgian case	- Single case study - Difficult to compare with FT cases in literature considering uniqueness of each case - No subjective and objective assessments on aesthetic outcome

Table 10.1: Summary of strengths and limitations of the current doctoral thesis.

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CHAPTER 11

Summary

Transplantation of body structures composed of tissues derived from different embryologic origin is known as composite tissue allotransplantation (CTA). It is a relatively new technique that has gradually evolved from the experience of solid organ transplantation and is the ultimate fusion of this technique with modern plastic reconstructive surgical techniques. Highly specialized structures that are otherwise impossible to reconstruct are repaired with anatomically identical structures to restore function, appearance and overall well-being in a single operation. Of all CTA procedures, facial transplantation (FT) has captured the exceptional interest and imagination of the medical community and the broad public since the first transplant in 2005.

After a preparatory phase of 2 years, we performed the first Belgian face transplantation in December 2011. This doctoral thesis addresses ethical, surgical, immunological, rehabilitation and psychological aspects involved in FT based on our experience and underscores the importance of a long-term multidisciplinary approach.

Chapter 1 outlines the history of human CTA. Of all involved structures in transplantation, skin and mucosa are the most antigenic. After dealing with many immunological issues, the first hand transplant was performed in 1998 and the first face transplant in 2005. Until now, 34 face transplants have been performed worldwide. An overview of results is given based on a systematic review of peer-reviewed literature. Overall outcome and satisfaction rate are good. Five deaths occurred due to non-compliance to the therapy, infection/sepsis and cancer recurrence. Selection and screening of the appropriate patient, well prepared surgical approach, intensive and early multidisciplinary rehabilitation, prompt treatment of complications and long-term follow-up by a large multidisciplinary team are the main factors for a successful outcome.

Chapter 2 describes our experience of establishing a facial CTA program at the Ghent University Hospital, Belgium. The whole process took about 2 years. Aspects of the guidelines of our program are discussed including the protocol, collaboration with the organ processing donor organization, patient selection, donor selection, organ procurement and donor surgery, the FT itself, immunosuppressive therapy, postoperative care, media and costs. A well-led multidisciplinary team composed of experts from diverse professional backgrounds and in which every member has a clearly defined role is the key to success.

Chapter 3 outlines the aims of the doctoral thesis and lists the thesis related publications.

After establishing the program in our hospital, the first successful facial CTA in Belgium was performed in December 2011 in a 55-year-old male patient with a central facial deformity and blindness after a ballistic injury. Temporary closure of the defect was achieved with a free plicated anterolateral thigh flap. In **chapter 4** the surgical, immunological, rehabilitation and psychological aspects of this transplantation are described. A digitally planned vascularized composite allotransplant of the lower 2/3rd of the face was performed. The patient experienced a single rejection period at week 15 treated successfully with corticoids. Intensive rehabilitation therapy started at week 1 postoperatively; sensory and motor recovery was noticed from month 4. Pre- and postoperative psychiatric and psychological support was provided to the patient and his family. We encountered several complications, mostly related to the immunosuppressive medication. The most severe complication was a pulmonary infection with *Aspergillus fumigatus.* Continuous multidisciplinary team approach ensured adequate management with several infectious and medical problems occurring until 13 months postoperatively. Two years postoperatively, the patient and his family are very satisfied with the overall outcome and social reintegration in the community is successful. Despite blindness, no issues were observed with compliance to rehabilitation, surveillance of the graft, and identity transfer.

Comparison between the functional outcomes of documented face transplant cases is very difficult as very few reports document detailed analyses regarding overall intelligibility, speech characteristics and oromyofunctional behavior.

Chapter 5 describes the 1-year outcome regarding speech and oromyofunctional behavior and **chapter 6** documents the longitudinal progress of the same parameters over 21 months postoperative. At 12 months post transplantation, overall intelligibility is normal in isolated words, but slightly impaired in sentences and spontaneous speech due to a moderate hypernasality caused by a fistula between the hard and soft palate. Phonetic inventory is complete. Vocal quality is normal, but articulation reveals phonetic disorders of mainly bilabials as a result of reduced lip functions. Over a period of 21 months post surgery, a longitudinal evolution of speech intelligibility, speech acceptability, voice, resonance, articulation and oromyofunctional behavior is seen. A detailed protocol for speech assessment after FT is described in order to better define speech rehabilitation for these unique patients in the future.

In facial transplantation functional nerve and muscle fibers replace the damaged tissues in the recipient. The success depends on adequate nerve sprouting in the grafted nerves and reinnervation of the muscles; only few reports are available on long-term results. In **chapter 7** the clinical and neurophysiological evolution of muscular recruitment during speech is described to evaluate axonal recovery and motor preparation two years after FT. Gradual increase of lip electromyography amplitude, reduction of reaction times and decrease of contingent negative variation amplitudes were seen paralleled by global improvement of lip motor function.

One of the goals of facial CTA is to improve quality of life and overall well-being of severely facial disfigured patients. Psychosocial functioning of the partner or of specific patient groups such as blind patients are less well investigated. **Chapter 8** documents positive psychological, marital and family functioning of our patient and his partner after FT. This underscores the importance of good psychosocial functioning pre transplantation of both partners and of their involvement in psychological and psychiatric treatment. The outcomes are also in favor for the expansion of inclusion criteria of FT to blind patients.

Of all 34 world-wide performed face transplant patients, there are only a few reports on follow-up more than 1 year postoperative. In **chapter 9** the 3-year outcome of our patient is described. The risk-benefit ratio of FT in this specific case is positive and the transplantation has been life changing psychologically. Anaplastology for both eyes and left upper eyelid resulted in a tremendous aesthetic improvement of the graft and should be considered as a very useful adjunctive tool for reconstitution of difficult to reconstruct facial structures such as ears and eyes. All components of speech intelligibility, in particular voice, resonance and articulation show a progressive and positive evolution. After a recurrence of the pulmonary *Aspergillus* infection at 31 months post transplantation, successfully treated, the overall medical situation is good and stable with minimal doses of triple immunosuppressive therapy only. Multidisciplinary team approach, intensive rehabilitation program and adequate treatment of complications have proven to be essential.

CHAPTER 12

Samenvatting

Transplantatie van lichaamsdelen opgebouwd uit weefsels van embryonaal verschillende oorsprong staat bekend als transplantatie van samengesteld weefsel (Composite Tissue Allotransplantation, CTA). Het betreft een relatief nieuwe techniek die progressief ontstaan is uit de ervaring rondom solide orgaan transplantatie (Solid Organ Transplantation, SOT) en is de ultieme fusie van deze techniek met moderne reconstructieve, plastisch chirurgische technieken. Uiterst gespecialiseerde lichaamsdelen die onmogelijk op een andere manier te reconstrueren zijn, worden vervangen door anatomisch identieke structuren afkomstig van een ander lichaam (de donor) teneinde herstel van functie, uiterlijk voorkomen en algemeen welbevinden te verkrijgen. Van alle CTA procedures heeft aangezichtstransplantatie veruit de grootste belangstelling opgewekt. Deze operatie heeft het meest tot de verbeelding gesproken van de medische wereld en van het brede publiek sinds de eerste transplantatie werd uitgevoerd in 2005.

Na een voorbereidende fase van 2 jaar hebben wij in december 2011 de eerste aangezichtstransplantatie in België uitgevoerd. Dit proefschrift behandelt de lange termijn multidisciplinaire aanpak van de chirurgische, ethische, immunologische, revalidatie en psychologische aspecten die relevant zijn bij aangezichtstransplantatie.

Hoofdstuk 1 beschrijft de geschiedenis van menselijk CTA. Van alle betrokken structuren in transplantatie zijn huid en slijmvliezen het meest antigeen. Nadat veel immunologische dilemma's werden opgelost, werd de eerste handtransplantatie uitgevoerd in 1998, gevolgd door de eerste aangezichtstransplantatie in 2005. Tot nu toe zijn wereldwijd 34 aangezichtstransplantaties uitgevoerd. Een overzicht van de resultaten van deze gevallen wordt gegeven op basis van een systematisch nazicht van *peer-reviewed* literatuur. De algemene resultaten, zowel chirurgisch als op vlak van tevredenheid zijn goed. Er werden 5 sterfgevallen gerapporteerd, door therapie ontrouw, infectie/sepsis en recidief van kanker. De belangrijkste factoren voor een geslaagd resultaat zijn selectie en screening van de geschikte patiënt, een goed voorbereide chirurgische aanpak, intensieve en tijdige multidisciplinaire revalidatie, prompte behandeling van complicaties en langdurige follow-up door een groot multidisciplinair team.

Hoofdstuk 2 beschrijft onze ervaring met het opzetten van een aangezichts-CTA programma in het Universitair Ziekenhuis Gent, België. Het hele proces nam bijna 2 jaar in beslag. De verschillende richtlijnen in ons programma worden besproken zoals het protocol, samenwerking met de donor organisaties, selectie van de patiënt, selectie van de donor, orgaan prelevatie en donor chirurgie, de eigenlijke aangezichtstransplantatie, de immunosuppressieve therapie, de postoperatieve zorg, het omgaan met de media en de kosten. Een goed geleid multidisciplinair team, samengesteld uit leden vanuit de verschillende professionele disciplines, waarin elk lid een duidelijk omschreven rol heeft, is de sleutel tot succes.

In **hoofdstuk 3** worden de doelstellingen van het proefschrift vermeld alsmede de publicaties gerelateerd aan het proefschrift.

Na het opzetten van het programma in ons ziekenhuis werd de eerste succesvolle aangezichtstransplantatie in België uitgevoerd in december 2011 bij een 55-jarige man met een centraal gelegen complex defect in het gelaat en blindheid na een ballistisch trauma. Een tijdelijke reconstructie werd eerst verkregen met een vrije anterolaterale dijbeen flap. In **hoofdstuk 4** worden de chirurgische, immunologische, revalidatie en psychologische aspecten van deze transplantatie beschreven. Een gevasculariseerd samengesteld weefsel transplantatie van het onderste tweederde deel van het gezicht werd uitgevoerd na pre-operatieve digitale planning. Er deed zich slechts één acute afstoting voor bij de patiënt 15 weken na de operatie, die met succes werd behandeld met corticosteroïden. Intensieve revalidatie therapie werd gestart 1 week na de operatie; herstel van gevoel en mimiek werd opgemerkt vanaf de 4e postoperatieve maand. De patiënt en zijn familie kregen pre- en postoperatieve psychiatrische en psychologische begeleiding. Er waren verschillende postoperatieve complicaties, vooral gerelateerd aan de immuunsuppressieve medicatie. De ernstigste complicatie was een longinfectie met *Aspergillus* *fumigatus.* Door continue multidisciplinaire team begeleiding was het mogelijk deze ernstige medische problemen, die tot 13 maanden na de transplantatie optraden, adequaat te behandelen. Twee jaar na de operatie zijn zowel de patiënt als zijn familie zeer tevreden over het resultaat. Ook de integratie in de maatschappij is volledig en succesvol. Ondanks blindheid bij de patiënt werden geen problemen gezien met de therapietrouw, klinische bewaking van het transplantaat of overdracht van identiteit.

Het vergelijken van functionele resultaten van gedocumenteerde aangezichtstransplantaties is erg moeilijk, omdat maar weinig publicaties rapporteren over gedetailleerde analyses betreffende algemene spraakverstaanbaarheid, kenmerken van spraak en oromyofunctioneel gedrag. **Hoofdstuk 5** beschrijft de 1-jaars uitkomst van spraak en oromyofunctioneel gedrag en **hoofdstuk 6** beschrijft het longitudinale verloop van dezelfde parameters tot 21 maanden postoperatief. Twaalf maanden na de transplantatie is de algemene spraakverstaanbaarheid normaal op woordniveau, maar licht beperkt in zinnen en spontane spraak als gevolg van een lichte hypernasaliteit te wijten aan een fistel tussen zacht en hard gehemelte. De fonetische inventaris is compleet. De kwaliteit van de stem is normaal, maar de articulatie vertoont fonetische stoornissen van voornamelijk de bilabialen door een beperkte lipfunctie. Gedurende 21 maanden na de operatie wordt een longitudinale evolutie van de spraakverstaanbaarheid, natuurlijkheid van de spraak, stem, resonantie, articulatie en oromyofunctioneel gedrag waargenomen. Er wordt een omschrijving gegeven voor een gedetailleerd protocol met de bedoeling in de toekomst spraak revalidatie beter te definiëren voor deze unieke patiënten.

Bij een aangezichtstransplantatie vervangen functionerende spieren en zenuwen de beschadigde weefsel in de ontvanger/recipiënt. Het succes hiervan is afhankelijk van zenuwregeneratie en reïnnervatie van de spieren. Er zijn slechts weinig artikelen beschikbaar met resultaten op lange termijn. In **hoofdstuk 7** wordt het klinische en neurofysiologische verloop van spier-recrutering tijdens spraak beschreven om het axonale herstel en motorische voorbereiding te evalueren 2 jaar na de aangezichtstransplantatie. Er werd een geleidelijke toename in amplitude van de lip electromyografie waargenomen, korter wordende reactietijden en afname van de contingent negatieve variatie amplitudes. Tegelijkertijd zagen we een globale verbetering van de motorische functies van de lip.

Eén van de doelstellingen van aangezichtstransplantatie is om de kwaliteit van het leven en algemeen welzijn te verbeteren van patiënten met een ernstige mutilatie van het gelaat. Het psychosociaal functioneren van de partner of van specifieke patiëntgroepen zoals blinde patiënten zijn onderwerpen die veel minder werden onderzocht. **Hoofdstuk 8** beschrijft positief psychologisch, echtelijk en familiaal functioneren van zowel patiënt als partner na de aangezichtstransplantatie. Dit onderzoek onderstreept het belang van goed psychosociaal functioneren voor de transplantatie van beide partners en hun betrokkenheid in de psychologische en psychiatrische behandeling. De uitkomsten pleiten ook voor een uitbreiding van de inclusie criteria voor blinde patiënten.

Van alle 34 aangezichtstransplantaties die wereldwijd werden uitgevoerd zijn maar weinig publicaties beschikbaar met een langere follow-up dan 1 jaar. In **hoofdstuk 9** worden de 3-jaars resultaten van onze patiënt beschreven. De voordelen hebben in dit specifieke geval duidelijk opgewogen tegen de risico's en de ingreep is psychologisch gezien levensverbeterend voor de patiënt geweest. Anaplastologie voor de beide ogen en het bovenste linker ooglid heeft geresulteerd in een spectaculaire esthetische verbetering van het transplantaat. Deze techniek moet beschouwd worden als een zeer waardevolle aanvulling bij aangezichtstransplantatie om moeilijk te reconstrueren onderdelen van het gezicht zoals ogen en oren te herstellen. Alle componenten van de spraakverstaanbaarheid, met name stem, resonantie en articulatie kennen een verdere positieve evolutie. Na een recidief van een *Aspergillus* longinfectie 31 maanden postoperatief, die succesvol behandeld werd, is er medisch gezien is een stabiele en gunstige situatie ontstaan waarbij patiënt alleen op lage onderhoudsdosis triple immunosuppressieve medicatie staat. Het is gebleken dat een multidisciplinaire team benadering, een intensief revalidatieprogramma en adequate behandeling van complicaties essentieel zijn voor succes.

CHAPTER 13

Résumé

La transplantation de parties du corps, composées de tissus d'origine embryonale différente, est connue sous le nom de transplantation composée (CTA). C'est une technique relativement récente qui trouve son origine dans la transplantation d'organes solides (SOT), et qui est l'ultime fusion de cette technique avec les techniques modernes de chirurgie reconstructrice et plastique. Des parties du corps hautement spécialisées, qui ne peuvent pas être reconstruites par d'autres techniques, peuvent être substituées par des structures anatomiques identiques provenant d' un autre corps (donneur), afin de reconstituer la fonction, l'apparence et le bien-être général. De toutes les techniques de CTA, la greffe faciale a suscité de loin le plus d'intérêt. Cette opération a impressionné le monde médical et le grand public depuis la première transplantation en 2005.

Après une phase préparatoire de 2 ans, nous avons exécuté la première transplantation faciale en Belgique en décembre 2011. Cette thèse décrit les aspects importants à long terme de l'approche multidisciplinaire, tant dans le domaine de l'approche chirurgicale, éthique, immunologique, la revalidation que les aspects psychologiques.

Chapitre 1 décrit l'histoire de la CTA humaine. De toutes les structures concernées dans la transplantation, la peau et le mucueuses sont les plus anti-géniques. Une fois nombre de dilemmes immunologiques résolus, la première transplantation de la main fut exécutée en 1998, suivi de la première transplantation de visage en 2005. Jusqu'à ce jour, 34 transplantations faciales ont eu lieu mondialement. Nous donnons un aperçu des résultats de ces cas basé sur une rétrospective systématique de la littérature *peer-reviewed*. En général les résultats, aussi bien au niveau chirurgical que de la satisfaction, sont bons. Cinq décès ont été rapportés, suit à un abandon de thérapie, infection/septicémie et récidive du cancer. Les facteurs primordiaux pour un bon résultat, sont une sélection et un screening du bon patient, une bonne préparation de l'approche chirurgicale, une revalidation multidisciplinaire et intensive en temps voulu, un traitement urgent des complications et un suivi prolongé par une équipe multidisciplinaire.

Chapitre 2 décrit notre expérience dans la création d'un programme de CTA-facial à l'Hôpital Universitaire de Gand en Belgique. Le processus complet a pris presque 2 ans. Les directives différentes sont décrites, tels le protocole, la collaboration avec les organisations de dons d'organes, la transplantation faciale en elle-même, la thérapie immuno-suppressive, les soins postopératoires, la gestion des médias et les coûts. Une équipe multidisciplinaire bien menée, composée de membres de disciplines différentes, ou chacun connaît son rôle est la clef du succès.

Chapitre 3 rapporte les buts de la thèse, ainsi que les publications en rapport avec celle-ci.

Après la création du programme dans notre clinique, la première transplantation faciale en Belgique a été réalisée en décembre 2011 chez un homme de 55 ans souffrant d'une lésion faciale complexe centrale, de cécité après un traumatisme balistique. Une reconstruction provisoire par lambeau libre de la cuisse antéro-latérale (ALT-flap) fut réalisée.

Chapitre 4 décrit les aspects chirurgicaux, immunologiques psychologiques et la revalidation de cette transplantation. Une greffe composée vascularisée des deux tier inférieures de la face fut réalisée après un planning préopératoire digital. Il n'y a eu qu'un seul épisode de rejet aigu chez le patient 15 semaines après l'intervention, un traitement par corticostéroïdes pu y mettre fin. Une revalidation intensive commença une semaine après l'intervention, nous avons constaté un rétablissement sensoriel et de la mimique à partir du 4ème mois postopératoire. Le patient et ses proches ont bénéficiés d'un suivi psychiatrique et psychologique. Il y a eu plusieurs complications postopératoires, surtout concernant les médicaments immuno-suppressifs. La complication majeure fut une pneumonie par *Aspergillus fumigatus*. Grâce à un suivi continu par l'équipe multidisciplinaire ces graves problèmes médicaux ont pu être traités jusqu'à 13 mois après la transplantation. Deux ans après la greffe, le patient et ses proches sont satisfaits du résultat. Malgré la cécité, nous n'avons pas constatés de problèmes liés à la fidélité thérapeutique, l'évaluation clinique de la greffe et la transmission d'identité.

La comparaison des résultats fonctionnels des transplantations documentées est difficile, car peu de publications rapportent des analyses détaillées concernant la perception de la parole, les caractéristiques de la parole ainsi que du comportement oro-myofonctionnel.

Chapitre 5 décrit le résultat après 1 an au niveau de la parole et du comportement oro-myo fonctionnel. **Chapitre 6** décrit l'évolution longitudinale des mêmes paramètres jusqu'à 21 mois postopératoires. Douze mois après l'opération l'intelligibilité générale de la parole est normale, elle est néanmoins limitée au niveau des phrases et la langue normale, suite à une hyper-nasalité provenant d'une fistule entre la palais moue et dur. L'inventaire phonétique est complet. La qualité vocale est normale, mais l'articulation démontre des perturbations phonétiques, particulièrement des bilabiales suite à une fonction labiale réduite. Pendant les 21 mois qui suivent l'opération nous constatons une évolution longitudinale de l'intelligibilité de la parole, le naturel de la parole, la voix, la résonance, l'articulation et le comportement oromyofonctionel. Nous décrivons un protocole détaillé afin de mieux définir la revalidation de la parole dans le futur pour ces patients uniques.
Lors d'une transplantation faciale, nous remplaçons les tissus abimés du receveur par des muscles et des nerfs fonctionnants. Le succès dépend de la régénération des nerfs et de la réénervation musculaire. Peu d'articles sont disponibles rapportant des résultats à long terme.

Chapitre 7 décrit le court clinique et neurophysiologique du recrutement musculaire lors de la parole afin d'évaluer la récupération axonale ainsi que la préparation motrice pendant les 2 années suivant la transplantation. Nous constatons une augmentation progressive de l'amplitude electromyographique de la lèvre, une diminution des temps de réaction et enfin une diminution du contingent des amplitudes de variations négatives.

Un des buts de la transplantation faciale est d'améliorer la qualité de vie et le bien être général des patients atteint d'une mutilation faciale grave. Le fonctionnement psychosocial des proches ou de groupes de patients spécifiques tels les aveugles, est un sujet nettement moins recherché.

Chapitre 8 décrit le fonctionnement positif au niveau psychologique, conjugal et familial du patient et de son conjoint après la transplantation. Cette recherche souligne l'importance d'un bon fonctionnement psychosocial des deux conjoints avant la transplantation et leur participation dans le traitement psychologique et psychiatrique. Les résultats plaident pour un élargissement des critères d'admission aux patients aveugles.
De 34 transplantations faciales réalisées au niveau mondial, nous disposons de peu de publications comportant un suivi de plus d'un an.

Chapitre 9 décrit les résultats à 3 ans de notre patient. Les avantages ont eu raisons des risques dans ce cas précis et l'intervention a amélioré la qualité de vie du patient au niveau psychologique. Un anaplastologie des deux yeux et une correction de la paupière supérieure de l'œil gauche ont spectaculairement amélioré l'apparence esthétique de la greffe. Cette technique doit être considérée comme une adjonction très valable lors d'une reconstruction faciale afin d'aider à reconstruire des structures difficiles tels les yeux et les oreilles. Toutes les composantes de l'intelligibilité de la parole, tels la voix, la résonance et l'articulation connaissent une amélioration continue. Après une récidive d'une pneumonie *Aspergillus* 31 mois postopératoire, traitée avec succès, une situation stable et favorable s'est établie, le patient ne devait plus prendre qu'une petite dose d'entretien de sa tri-thérapie immunosuppressive. Il est apparu qu'une approche d'une équipe multidisciplinaire, un programme de revalidation intensif et un traitement adéquat sont les clef du succès.

Success is the result of perfection, hard work,

learning from failure, loyalty and persistence

Colin Powel

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Curriculum vitae

Nathalie ROCHE (°July 27th 1967 Emmen, the Netherlands) studied Medicine in Rotterdam, the Netherlands, at the Erasmus University from 1985 until 1992. She trained in general and plastic surgery in Amsterdam (NL) and Ghent(B) and graduated in 2000 from the training program of the department of Plastic and Reconstructive Surgery in Ghent under guidance of Prof. Dr. Stan Monstrey, Prof. Dr. Phillip Blondeel and Prof. Dr. Koenraad van Landuyt. She successfully passed the final examinations and obtained the titles of Fellow of the Collegium Chirurgicum Plasticum and Fellow of the European Board of Plastic, Reconstructive and Aesthetic Surgery. From 2001 to 2004 she worked as full-time staff member in the department of Plastic Surgery in the Erasmus Medical Center in Rotterdam (NL), where she mainly performed pediatric plastic surgery, head and neck reconstructions and craniofacial surgery. From 2004 she works as Associate Professor in the department of Plastic Surgery of the Ghent University Hospital.

She is an active member of various international societies, such as the Royal Belgian Society of Plastic Surgery, the European Association of Plastic Surgeons, the Dutch Association for Cleft Palate and Craniofacial Anomalies and the American Society of Plastic Surgeons.

Nathalie Roche is author of numerous clinical and scientific papers and presented at several national and international meetings. She also performs charity work as a volunteer plastic surgeon in the developing countries for mainly cleft lip and palate and burn surgery.

Her main fields of interest are pediatric plastic surgery, breast reconstruction with autologous tissue, head and neck reconstructions and craniofacial surgery.

She has three children: Sebastiaan (°2000), Valérie(°2005) and Jonathan(°2006).

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